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嗜铬细胞瘤与副神经节瘤精准诊断进展

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【摘要】嗜铬细胞瘤/副神经节瘤 (PPGL) 是具有转移潜能的罕见神经内分泌肿瘤, 常因缺乏典型的临床症状被忽视。随着儿茶酚胺及其代谢产物测量方法和影像学成像方式的改进, PPGL 的诊断率呈上升趋势。但其精准诊断仍面临分子异质性显著、传统影像技术效能局限等核心挑战。本综述将阐明 PPGL 的发病机制、临床症状、诊断及分类, 以期为 PPGL 的诊断提供帮助。

【关键词】嗜铬细胞瘤; 副神经节瘤; 神经内分泌肿瘤; 转移性疾病

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Progress in precision diagnosis of pheochromocytoma and paraganglioma

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【Abstract】Pheochromocytoma / paraganglioma (PPGL) is a rare neuroendocrine tumor with metastatic potential that is often overlooked due to atypical clinical presentations. With advances in biochemical assays for catecholamines and their metabolites, combined with improved imaging techniques, the diagnostic rate of PPGL has been steadily increasing. Nevertheless, precise diagnosis continues to face major challenges including significant molecular heterogeneity and the limited sensitivity of conventional imaging modalities. This review systematically elucidates the pathogenesis, clinical manifestations, diagnostic approaches, and classification systems of PPGL, aiming to support and improve its diagnosis.

【Keywords】Pheochromocytoma; Paraganglioma; Neuroendocrine tumors; Metastatic diseases

0 引言

嗜铬细胞瘤和副神经节瘤统称为嗜铬细胞瘤/副神经节瘤 (Pheochromocytoma and Paraganglioma, PPGL), 是一类具有转移潜能的罕见神经内分泌肿瘤^[1]。PPGL 年发病率为 2.0~8.0 例/百万, 但流行病学数据显示其发生率呈上升趋势^[2-3]。PPGL 缺

乏特异性临床表现, 约 10%~20% 的 PPGL 患者会发生转移, 但目前缺乏可靠的恶性预测标志物能在初诊时准确预测肿瘤生物学行为^[4]。传统依赖儿茶酚胺及其代谢产物的生化检测受多种因素干扰 (如药物、肾功能)^[5]。遗传异质性干扰诊断策略, 不同基因型的肿瘤具有差异化的分泌特征和影像学表现, 导致统一诊断标准难以适应^[6]。上述因素均导

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致PPGL的早期诊断仍面临诸多挑战。近年来随着生化测试的改进、影像学技术的优化、遗传和分子诊断的深入等关键领域的进步, PPGL的诊断取得了巨大进展^[4-5, 7-10]。本文通过系统综述PPGL诊断进展, 旨在为临床实践提供参考依据。

1 发病机制

PPGL的分子发病机制与基因种系突变密切相关。研究表明, 35%~40%的PPGL患者携带已知的肿瘤易感基因种系突变^[11-12]。基于致癌信号通路激活模式, 国际共识将PPGL分为3个分子亚型: 假性缺氧组(Cluster 1, 10%~15%)以琥珀酸脱氢酶复合体(Succinate Dehydrogenase Complex, SDHx)基因(*SDHA* / *SDHB* / *SDHC* / *SDHD* / *SDHAF2*)及*VHL/EGLN1/HIF2A*突变为特征, 通过稳定缺氧诱导因子-1 α 驱动血管生成^[13-14]; 激酶信号组(Cluster 2, 50%~60%)涉及*RET/NF1/MAX/TMEM127*等基因突变, 通过ERK/MAPK和PI3K-AKT-mTOR通路促进细胞增殖^[15]; Wnt信号组(Cluster 3, 5%~10%)以*CSDE1/MAML3*融合基因为标志, 与上皮-间质转化和远处转移相关^[16-17]。近年来还报道了一些新的驱动基因和变异机制。无已知易感基因突变时, 有研究报告, 种系渐变性淋巴瘤激酶(Anaplastic Lymphoma Kinase, ALK)突变可能为PPGL的驱动因素, 提示新靶点治疗(如ALK抑制剂)的可能性^[18]。BRAF-containing融合转录体在PPGL发病机制中也被初步描述, 可能通过激活MAPK信号通路促进肿瘤形成^[19]。*EPAS1*变异导致稳定缺氧诱导因子-2 α 失调, 参与氧传感和血管生成路径, 部分解释了PPGL与红系异常的关联^[20]。

*SDHx*基因(包括*SDHA*、*SDHB*、*SDHC*和*SDHD*)是最常见的遗传易感基因, 约20%的PPGL患者携带*SDHx*基因种系突变^[21-22]。其中*SDHB*基因种系突变(c.724C>T等热点变异)与侵袭性表型显著相关^[23-24]。多中心研究表明, 成人转移性嗜铬细胞瘤/副神经节瘤(metastatic Pheochromocytoma and Paraganglioma, mPPGL)中*SDHB*突变率达58.7% (95%CI: 52.4~64.9), 且携带p.Arg90Ter无义突变者的5年转移风险较野生型增加3.2倍($HR=3.2$, $P<0.001$)^[17, 25]。分子机制研究证实, *SDHB*缺陷通过抑制组蛋白去甲基化酶KDM4, 导致H3K9me3异常积累和转移相关基因(如*MMP2*)的异常激活^[26]。*SDHB*突变呈常染色体显性遗传, 一级亲属的遗传风险高达50%, 致病性变异携带者

终身存在PPGL及其他相关肿瘤风险^[27]。因此, 2014年内分泌学会和2021年北美神经内分泌肿瘤学会指南建议对所有初诊PPGL患者考虑进行包含*SDHx*的16基因panel检测, 并对确诊mPPGL者开展家系筛查^[28-30]。检测需覆盖*SDHA*、*SDHB*、*SDHC*、*SDHD* 4个亚基因的致病性变异(如错义突变、无义突变、插入缺失等)^[31-32]。*SDHB*突变携带者的家族成员(尤其是一级亲属)应接受定期遗传检测或*SDHB*筛查, 以实现早期发现和干预^[33]。

2 临床表现

PPGL的临床表现呈现显著解剖功能异质性, 主要受肿瘤神经嵴起源(交感/副交感神经节)、儿茶酚胺分泌状态及转移灶分布模式影响。交感神经源性肿瘤多位于腹部和盆腔, 持续分泌去甲肾上腺素导致90%以上患者出现阵发性高血压, 其中10%进展为高血压危象, 典型三联征(头痛71%、心悸65%、多汗65%)具有重要诊断提示价值^[2]。值得注意的是, 过量儿茶酚胺可诱发多种非典型临床表现, 包括Takotsubo心肌病(11%)、急性肠系膜缺血(7.2%)及代谢性脑病等^[34]。

与之相对, 副交感神经源性肿瘤(多见于头颈部)常表现为生物学寂静性, 60%患者初诊时已发生转移, 其隐匿性进展模式导致平均诊断延迟达28个月^[35]。此类病例多因转移灶压迫症状(如骨痛、肝功能障碍)或影像学偶然发现而确诊, 凸显建立基于分子标志物的早期筛查体系的重要性^[36]。

3 诊断

PPGL的诊断需综合临床表现、生化检测、影像学及组织病理学。

3.1 生化检测

生化检测的核心在于对神经内分泌代谢通路的精准解析。肿瘤细胞异常分泌的儿茶酚胺类物质及其衍生物构成了诊断金标准, 其代谢谱系呈现典型时空特征: 原型物质(肾上腺素、去甲肾上腺素、多巴胺)→中间代谢产物[甲氧基去甲肾上腺素(Normetanephrine, NMN)、甲氧基肾上腺素(Metanephrine, MN)、3-甲氧基酪胺]→终末代谢产物(香草扁桃酸、高香草酸)^[37]。值得强调的是, NMN/MN的肿瘤特异性代谢特征源于PPGL组织内儿茶酚-O-甲基转移酶的持续活化, 这种酶促动力学特性使其具有表达稳定优势(半衰期>24 h), 显著优于原型儿茶酚胺的瞬态波动性^[38-39]。

基于国际多中心研究证据, 现行诊断共识确立

NMN/MN 为双核心生物标志物。其诊断效能经 Meta 分析证实: 血浆游离 NMN/MN 联合检测灵敏度达 96.8% (95%CI: 93.2 ~ 98.5), 特异度提升至 94.3% (95%CI: 89.7 ~ 97.1) [39]。在方法学选择上, 液相色谱串联质谱因其卓越的分子分辨能力 (质量精度 <2 ppm) 和抗基质干扰特性, 被内分泌学会临床实践指南列为推荐检测方案 [40-41]。值得注意的是, 当血浆 NMN/MN 浓度超过阈值 ($\geq 2 \times \text{ULN}$) 时, 其阳性预测值可达 98.6%, 此时应立即启动影像学验证流程 [37, 39]。

除核心代谢标志物外, 新型分子标志物的临床应用价值日益凸显: (1) 嗜铬粒蛋白 A (CgA): 作为神经内分泌颗粒基质蛋白, 其异常升高与 PPGL 恶性转化风险显著相关 ($OR=7.32$, 95%CI: 4.15 ~ 12.91)。研究证实, CgA 与 MN 联合检测可突破无功能性 PPGL 的诊断瓶颈, 使灵敏度达 100% (特异性 89.3%), 且其动态变化与肿瘤负荷呈显著正相关关系 ($r=0.82$, $P<0.001$) [42-43]。(2) 神经元特异性烯醇化酶: 作为糖酵解关键酶, 其血清水平升高 ($>15 \text{ ng/mL}$) 提示 PPGL 可能伴神经内分泌分化, 在复合型肿瘤鉴别中具有重要价值 [42]。

3.2 影像诊断

3.2.1 解剖成像

计算机断层扫描 (Computed Tomography, CT) 作为 PPGL 定位诊断的首选影像学手段, 其优势体现在快速成像能力 (平均扫描时间 <2 min) 和较高的空间分辨率 (层厚可达 0.5 mm) [44]。研究证实, CT 对胸腹腔盆腔原发灶的检出敏感性达 93% ~ 100%, 但其特异性仅 70%, 可能与类圆形软组织密度影 (平均 CT 值 35 ~ 50 HU) 的影像特征有关, 这些病灶常呈现富血供强化模式 (增强后 CT 值提升 $>50 \text{ HU}$), 并伴有特征性囊变区 (约 30%) 及斑点状钙化 (约 15%) [45]。值得注意的是, CT 在检测 $<5 \text{ mm}$ 转移灶及早期复发 (术后 6 个月内) 方面存在局限性, 其敏感性下降至 68% [44]。

磁共振成像 (Magnetic Resonance Imaging, MRI) 凭借其多参数成像特性 (T1/T2/DWI/动态增强), 在血管侵犯评估 (敏感度 92%) 和肝转移检测 (敏感度 95%) 方面具有优势。典型 PPGL 在 T2WI 呈现灯泡征 (信号强度比 >3.0), 而 T1WI 低信号背景下出现亚急性出血灶 (正铁血红蛋白形成) 可呈现特征性高信号 [45]。研究表明, 脂肪抑制序列对腹膜后副神经节瘤的鉴别诊断具有较高价值 ($AUC=0.87$), 但需注意约 8% 病例因瘤内脂肪变性可能导致信号异质性, 这种信号异质性可能与肿瘤

基质成分差异相关 [44]。

3.2.2 功能成像

3.2.2.1 $^{131}\text{I}/^{123}\text{I}$ -MIBG 扫描

放射性示踪剂间碘苄胍 (Metaiodobenzylguanidine, MIBG) 作为去甲肾上腺素的结构同源物, 通过囊泡单胺转运体介导的主动运输机制实现肿瘤特异性聚集 [46]。其放射性同位素标志物 ($^{131}\text{I}/^{123}\text{I}$ -MIBG) 在分子影像学领域展现出差异化的应用特征: ^{123}I -MIBG 因其 γ 射线能量 (159 keV) 适宜于单光子发射计算机断层扫描 (Single Photon Emission Computed Tomography, SPECT) 显像, 在肿瘤定位诊断中具有更优的空间分辨率; 而 ^{131}I -MIBG 凭借 β 射线特性, 在治疗前剂量学评估及治疗后生物分布特征记录方面具有独特优势 [47]。

临床研究数据表明, 放射性同位素标志物 ($^{131}\text{I}/^{123}\text{I}$ -MIBG) 成像技术的诊断准确性呈现显著的疾病分型依赖。多中心荟萃分析显示, 其对局限型 PPGLs 的病灶检出率可达 96% (95%CI: 92% ~ 98%), 但对转移性病变的敏感性降低至 79% (95%CI: 71% ~ 86%) [48-49]。这种诊断效能的降低可能与肿瘤微环境演变相关: *SDHx* 基因突变介导的儿茶酚胺合成酶表达抑制可导致囊泡单胺转运体密度显著下调; 同时, 肿瘤细胞去分化过程引发的去甲肾上腺素转运体功能失活, 可能造成显像剂摄取障碍 [50-51]。

在临床应用评估中需重视其局限性: 首先, 肉芽肿性病变 (如结核或结节病) 及部分神经内分泌肿瘤亚型 (如胃肠间质瘤或分泌型肿瘤) 可能出现示踪剂非特异性摄取, 导致假阳性结果 [52-53]; 其次, 对于头颈部小病灶 ($<1 \text{ cm}$) 及位于复杂部位 (如颅底或颈动脉分叉部位) 头颈部副神经节瘤 (Head and Neck Paragangliomas, HNPGs) 及多发性内分泌腺瘤病相关病例易出现假阴性结果 [54-56]。MIBG 显像的适应证主要聚焦于: 生化指标存疑病例的辅助验证、遗传性 PPGL 综合征的系统筛查、 ^{131}I -MIBG 放射配体治疗候选者评估, 以及术后复发监测等临床场景 [57-59]。

3.2.2.2 生长抑素受体成像技术

神经内分泌肿瘤的特征性分子标志物——生长抑素受体 (Somatostatin Receptor, SSTR) 作为跨膜糖蛋白复合体, 在肿瘤细胞膜上呈现特异性高表达模式。分子影像学研究发现, 经放射性标记的 SSTR 配体 (如多肽类化合物) 与特定受体亚型 (SSTR2/SSTR5) 显示出优异的选择性结合能力 [60-61]。基于分子靶向识别机制, 通过 SPECT/

CT与正电子发射断层扫描 (Positron Emission Tomography, PET)/CT成像融合技术, 可精准捕获配体-受体复合物的空间分布特征, 为功能代谢显像提供定量依据。以 ^{68}Ga -DOTATATE为代表的奥曲肽类显影剂, 其空间分辨率较传统MIBG显像显著提升 (特异性99% vs. 70%~85%), 对不同解剖部位 (如头颈部HNPGL和转移病灶) 和特定基因突变 (如 $SDHx$) 的PPGL展现出高检出率^[62-63]。一项针对14例HNPGLs患者的研究显示, 使用 ^{68}Ga -DOTATOC PET/CT进行成像, 42.9%的患者诊断为颈静脉副神经节瘤, 并能精准显示肿瘤边界和表达水平, 特别适用于术前评估和治疗规划^[64]。肾上腺嗜铬细胞瘤的SSTR2阳性率达到100%, ^{68}Ga -DOTA-TATE在肾上腺部位表现出显著更优的敏感性和特异性, 这使得SSTR成像成为肾上腺PPGL的金标准^[65-66]。胰腺、小肠/肠系膜等功能部位的副神经节瘤SSTR2阳性率分别为81.2%和66.7%, 表明SSTR成像在这些部位具有较高的灵敏度和阴性预测值^[65]。然而在肺和骨转移等部位, SSTR2阳性率仅为9.1%^[65]。PPGL的分子异质性 (如 $SDHx$ 基因突变) 直接影响SSTR成像的性能。研究显示, $SDHx$ 突变导致线粒体功能障碍, 增加SSTR表达, 从而使SSTR成像成为首选^[67]。更具转化意义的是, 基于显像剂摄取异质性建立的定量模型 (如最大标准化摄取值、TL参数), 可为肽受体放射性核素治疗的适用性评估提供动态生物学标志^[68-69], 推动诊疗决策从形态学评估向分子表型指导的范式转变。

3.2.2.3 PET/CT

PET/CT相较于传统MIBG显像及生长抑素受体显像技术, 在PPGL的病灶识别中展现出更优的检测效能。当前临床应用的靶向显影剂涵盖多类生物标志物探针, 包括: 儿茶酚胺代谢通路示踪剂 (如 ^{18}F 标记氟苄胍、 ^{11}C -羟基麻黄碱)、神经递质前体类似物 (如 ^{18}F -FDOPA) 以及生长抑素受体特异性配体 (如 ^{68}Ga 标记DOTATATE复合物) 等^[70-72]。基于正电子湮灭辐射原理的 ^{18}F 同位素显像系统具备亚毫米级空间分辨率, 其病灶定位准确性和生物标志物特异性已被多项多中心研究验证, 尤其适用于多灶性病变、转移性病灶及 $SDHB$ 基因突变相关病例的影像学评估^[73-74]。

肿瘤微环境特征显著影响显影剂选择策略。PPGL病灶因缺氧诱导因子激活导致的瓦伯格效应, 使得 ^{18}F -FDG PET在葡萄糖代谢显像中呈现特征性

标准摄取值变化。研究显示该技术对mPPGL的检出敏感度为50%~100%, 常规PPGL诊断敏感度为76.8%~88.0%^[75-77]。值得注意的是, 生长抑素受体亚型表达特征使 ^{68}Ga -DOTATATE PET成为分子分型的重要工具, 其病灶检出率较 ^{18}F -FDG显像提升23.6% ($P<0.05$), 在肾上腺外副神经节瘤诊断中更具优势^[78]。此外, 该显像技术对肽受体放射性核素治疗的疗效预测价值, 已纳入美国国家综合癌症网络临床实践指南作为治疗前评估的推荐^[79], 但其临床应用仍受限于价格及PET/CT设备的可及性。

在PPGL的影像学诊断中, 不同的成像模式具有各自独特的优势和局限性。例如解剖成像: CT快速普及, 增强扫描可显示肾上腺病变富血供特征, 但对亚厘米病灶或囊性变敏感性不足^[80]; MRI无辐射, 软组织对比度更优, 尤其适用于头颈/脊柱旁病变, 但骨转移检出弱于CT^[81]。功能成像技术: MIBG显像 ($^{123}\text{I}/^{131}\text{I}$ -MIBG) 特异性高, 对恶性PPGL检出率约85%, 但敏感性受限且空间分辨率低^[82]; ^{68}Ga -DOTATATE PET/CT对转移性PPGL (尤其 $SDHx$ 突变相关SSTR高表达型) 敏感性高, 但非SSTR高表达肿瘤 (如部分散发型) 可能漏诊^[54, 83]; ^{18}F -FDG PET/CT适用于SSTR阴性而CT阳性的不匹配病灶, 但对低级别PPGL特异性低, 易与高代谢病灶混淆^[84]。PPGL的影像学选择需基于肿瘤生物学特征 (如SSTR表达、遗传背景)、临床需求 (分期、治疗规划) 及技术可用性进行个体化选择。 ^{68}Ga -DOTATATE PET/CT是目前转移性PPGL的首选功能成像方法, 而MIBG显像在治疗筛选中具有不可替代性^[54, 85]。解剖成像 (CT/MRI) 仍是定位基础^[80]。建议采用多模态整合策略, 如解剖联合功能成像: MRI/CT联合PET (例如 ^{68}Ga -DOTATATE PET/CT或 ^{18}F -FDG PET/CT) 可提高微小病灶的检出率^[86-87]。对于疑难病例, 联合多种示踪剂, 如SSTR和FDG示踪剂 (如 ^{68}Ga -DOTATATE+ ^{18}F -FDG) 可覆盖不同代谢表型^[88-89]。此外, 还可以优化流程, 以期最大化提高诊断准确性。

3.3 病理诊断

PPGL组织病理学诊断仍是诊断的金标准, 其组织学特征表现为肿瘤细胞呈巢状或小叶状排列 (Zellballen结构), 周围由支持细胞包裹。细胞核异型性可能提示恶性潜能, 但组织学良、恶性难以仅凭形态学判断^[90-92]。良、恶性生物学行为的异质性判读需突破传统形态学局限, 确诊需严格遵循

世界卫生组织指南中关于恶性PPGL的界定标准,即存在非嗜铬系统转移灶这一金标准^[17,93]。在标志物应用层面,神经内分泌谱系标志物(CgA、Synaptophysin)与间质支持细胞标志物S-100蛋白构成诊断基础^[94-96]。值得注意的是,SDHB作为SDHx基因突变的替代标志物,其表达缺失不仅具有92.3%的突变预测价值^[97-98],更与高肾上腺嗜铬细胞瘤与副神经节瘤分级(Grading of Adrenal Pheochromocytoma and Paraganglioma, GAPP)评分显著相关,提示肿瘤细胞去分化程度与转移风险的正向关联^[17,99]。在预后评估方面,改良版GAPP评分系统通过整合组织分化等级(良好/中度/差)、坏死程度及血管侵犯等量化指标,构建了分层预后模型:5年生存率低危组(0~2分)92% vs. 高危组(4~6分)47%,这一评估体系较传统Ki-67指数更能反映肿瘤生物学本质^[17,99-102]。

特定胚系或体细胞基因突变(如SDHx复合物亚基失活突变)通过驱动独特的代谢重编程(如琥珀酸累积诱导伪缺氧通路)和受体/转运体表达谱差异(如生长抑素受体过表达),显著影响PPGL的分子功能显像特征。这使得基于⁶⁸Ga-DOTATOC、¹⁸F-FDOPA等靶向显像剂的摄取模式可实现不同分子亚型的无创鉴别^[20,87,103-104]。然而,当前影像学指标尚未被证实能直接预测肿瘤病理分级或转移潜能。未来研究需整合放射组学特征与基因组学、代谢组学等多维数据,以建立更精准的影像生物标志物体系用于风险分层^[87,105-106]。

4 总结

PPGL作为一类具有恶性转化潜能的神内分泌肿瘤,其临床管理仍面临重要挑战,全球发病率呈上升趋势,临床症状高度隐匿;胚系致病基因突变显著影响肿瘤生物学行为及临床转归。尽管基于儿茶酚胺代谢谱分析及多模态影像学提升了诊断效能,但现有诊疗体系仍面临重大瓶颈:(1)分子分型与表型的关联机制尚未完全阐明;(2)传统影像学对微转移灶识别不足;(3)基于组织病理学的GAPP分级系统对预后评估存在误判风险。建议建立“基因型-表型-影像型”三位一体的诊断策略,基因型先行,全面遗传分型,所有PPGL患者(无论散发性或家族性)应进行系统性基因分型。在明确基因型后,进行多维度表型分析,包括临床表型(患者年龄、肿瘤位置、转移状态)、生化表型(儿茶酚胺代谢物水平等)及细胞特征(受体表达或细胞特性)。基于基因型和表型选择并定制影像路径,

最后结合计算模型和多学科协作实现精准化诊断。从而推动从传统形态学诊断向精准分子分型的范式转变。

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