·综述·

PET/CT 技术在阿尔茨海默病诊疗研究中的进展

朱文悦[1,2]，李夏春[1,2,3]
（1. 三峡大学基础医学院机能学部，湖北 宜昌 443002；2. 三峡大学精神卫生研究所，湖北 宜昌 443002；
3. 三峡大学肿瘤微环境实验室，湖北 宜昌 443002）

摘　要：随着人口老龄化加剧，我国痴呆人口比例急剧上升，给家庭和社会带来沉重的经济和照护负担。阿尔茨海默病（AD）是一种老年期发病的进行性认知障碍疾病谱，表现为记忆减退、注意力和执行力下降，在疾病晚期甚至发展为痴呆，最终导致生活自理能力丧失，进一步加重家庭和社会压力。AD 患者可处于数十年以上并无明显临床认知下降表现的临床前阶段，但脑中已存在显著病理变化，包括β淀粉样蛋白（Aβ）聚集形成老年斑、tau 蛋白过度磷酸化聚集形成神经元纤维缠结，血管淀粉样蛋白沉积、突触和神经元丢失，以及神经炎症。这一阶段是 AD 早期干预的最佳时机，准确诊断或预测 AD 风险并施以干预措施，可显著延缓或阻止 AD 进展。近年来多种追踪 AD 神经病理变化的示踪剂在 PET/CT 中的应用，使临床前 AD 及早期 AD 的影像诊断、治疗监测及预后预测的临床研究取得显著进展。本文将综述以 Aβ、tau 蛋白、氟代脱氧葡萄糖（FDG）、突触和炎症为示踪剂标记的 PET/CT 及 PET/MR 技术在 AD 早期诊断、鉴别诊断、疾病分期、治疗监测和预后预测的应用，并比较这些示踪剂作为生物标志物的相对效用和局限性，为临床医生在前驱期 AD 及 AD 早期诊疗研究中选择合适的 PET 标志物提供依据与参考。

关键词：PET/CT；阿尔茨海默病；示踪剂；PET/MR；早期诊疗
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Advances on PET/CT for the diagnosis and treatment of Alzheimer´s disease

ZHU Wenyue[1,2], LI Xiachun[1,2,3]
（1. Department of Functional Sciences, School of Basic Medicine, China Three Gorges University, Yichang 443002, China; 2. Institute of Mental Health, China Three Gorges University, Yichang 443002, China; 3. Tumor Microenvironment Laboratory, China Three Gorges University, Yichang 443002, China）
Correspondence to: LI Xiachun; E-mail: 624275550@qq.com

Abstract: With the intensification of population aging, the proportion of people with dementia in our country is rising sharply, bringing a heavy economic and caregiving burden to families and society. Alzheimer's disease (AD) is a spectrum of progressive cognitive impairment disorders that onset in old age, characterized by memory decline, reduced attention and executive function, and in the late stages of the disease, it can even progress to dementia, ultimately leading to the loss of self-care abilities and further increasing the pressure on families and society. Patients with Alzheimer's disease (AD) can be in a preclinical stage for decades without obvious clinical cognitive decline, but significant pathological changes have already occurred in the brain, including the aggregation of beta-amyloid (Aβ) to form senile plaques, the hyperphosphorylation and aggregation of tau protein to form neurofibrillary tangles, vascular amyloid deposition, synaptic and neuronal loss, as well as neuroinflammation. This stage represents the best opportunity for early intervention in AD. Accurate diagnosis or prediction of AD risk and implementation of intervention measures can significantly delay or prevent the progression of AD. In recent years, the application of various tracers that track the neuropathological changes of AD in PET/CT has led to significant progress in clinical research on the imaging diagnosis, treatment monitoring, and prognostic prediction of preclinical and early-stage AD. This article will review the application of PET/CT and PET/MR techniques

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作者简介：朱文悦，第一作者，研究方向：神经精神疾病影像诊断，E-mail：1951273792@qq.com；李夏春，通信作者，副教授，研究方向：阿尔茨海默病早期诊断，E-mail：624275550@qq.com

marked with Aβ, tau protein, fluorodeoxyglucose (FDG), synaptic, and inflammatory tracers in the early diagnosis, differential diagnosis, disease staging, treatment monitoring, and prognostic prediction of AD, and compare the relative utility and limitations of these tracers as biomarkers, providing a basis and reference for clinicians to choose appropriate PET markers in the research of early diagnosis and treatment of preclinical AD and early-stage AD.

Key words: PET/CT; Alzheimer's disease; tracers; PET/MR; early diagnosis and treatment

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随着人口老龄化程度不断加深，神经退行性疾病所带来的沉重负担愈发受到社会的广泛关注。阿尔茨海默病(Alzheimer ' s disease, AD)是一种在老年期和老年前期发病，以进行性记忆减退、注意力和执行力下降，甚至痴呆为主要特征的认知障碍疾病谱。AD疾病谱包括AD临床前阶段(preclinical stages of AD, PCS-AD)、轻度认知障碍(mild cognitive impairment, MCI)阶段和痴呆阶段。PCS-AD可持续数十年以上，以神经病理变化为主，常无显著认知下降表现或仅表现为主观认知下降(subjective cognitive decline, SCD)[1]。AD脑的核心病理特征是细胞外β-淀粉样蛋白(β-amyloid, Aβ)斑块、神经元内tau聚集体形成的神经原纤维缠结(neurofibrillary tangles, NFT)，并伴有血管淀粉样蛋白沉积、突触和神经元丢失，以及神经炎症和反应性星形胶质细胞增生症。Braak分级根据Aβ斑块的分布分为Ⅰ~Ⅵ级，Ⅰ级限于新皮层，Ⅱ级扩至内嗅皮层，Ⅲ级分布至间脑、纹状体、基底前脑胆碱核，Ⅳ级达中脑和延髓，Ⅴ级波及小脑，Ⅵ级病变达原始感觉皮层，Ⅳ、Ⅴ级AD病变基本有AD症状[2]。Braak分级根据脑内NFT有无及分布范围分为Ⅰ~Ⅵ级。AD神经病理变化分级采用ABC评分系统，分别对Aβ斑块(A)、NFT(B)、神经炎斑块(neuritic plaques, NPs;C)进行独立评估，其具体分级标准为A0~A3，B0~B3，C0~C3，根据这些分级，最终整合为无、低、中、高级这4个神经病理诊断[3]。因此，反映AD早期病理变化的各种血液、脑脊液生物标志物，以及影像学检查，均为PCS-AD的早期诊断提供了可能性。尽管低成本、无放射性的生物标志物近年在AD诊疗研究中备受重视，但其有创性和低重复性使其并未在临床诊疗广泛应用。计算机断层扫描(computed tomography, CT)及核磁共振成像(magnetic resonance imaging, MRI)对PCS-AD病理变化的低敏感性也使其临床价值受限。近年来，可反映AD病变的示踪剂的PET/CT技术在AD诊疗研究的应用提高了AD早期诊断和治疗的精准性。本文将系统回顾以Aβ、tau、氟代脱氧葡萄糖(fluorodeoxyglucose, FDG)、突触和神经炎症为示踪剂的正电子发射计算机断层显像(positron emission tomographic, PET/CT)及PET/MR成像技术在AD疾病谱中的诊断、治疗监测及预后预测的应用优势与局限，为临床医生在早期AD诊疗研究中提供科学依据，以帮助其合理选择最合适的成像技术。

1　Aβ PET的临床应用价值及局限

1.1　Aβ PET对AD和MCI的诊断价值

1.1.1　一代PIB对AD和MCI的诊断价值　^{11}C-标记的匹兹堡化合物B(Pittsburgh Compound B, PIB)是硫代磺素的衍生物，能快速通过血脑屏障，敏感特异结合纤维状Aβ及淀粉样血管病的Aβ;PIB在AD的后扣带回、顶叶和额叶皮质的沉积，诊断AD的准确率高，但诊断MCI的准确率却较低(仅48% MCI有AD样PIB摄取)[4]。PIB的非特异性脑白质摄取会随着年龄增长而增加，在高龄患者中，其灰白质对比度逐渐降低，这使得在采用视觉读数评估认知未受损(cognitive unimpaired, CU)的年轻患者时，容易出现Aβ病变的假阳性结果[5]。此外，PIB仅有的20 min半衰期也限制了其在临床中的广泛应用。

1.1.2　二代硫磺素类Aβ探针对AD和MCI的诊断价值　二代PIB类示踪剂^{18}F-Florbetapir (^{18}F-AV45)、^{18}F-flutemetamol (^{18}F-FMM)和^{18}F-florbetaben (^{18}F-FBB)在新皮层的沉积相似，且半衰期均为110 min，已被FDA批准用于临床应用。^{18}F-AV45在新皮层、扣带回，楔前叶高摄取，测定AD的中高度Aβ病变的灵敏度和特异性高，与Aβ42/Aβ40的诊断一致性高[6]。^{18}F-AV45在楔前扣带回及后扣带回的高摄取，与执行功能受损相关，可辅助诊断执行功能受损的AD亚型[7]。Meta分析显示，^{18}F-AV45和^{11}C-PIB诊断AD和AD-MCI的整体效能相似，亚组分析显示AβPET诊断AD的敏感性和特异

性高(0.91, 0.84),区分MCI和AD的特异性低(0.49)[8]。^{18}F-FMM能高效区别MCI和AD(受试者工作特征曲线下面积AUC为0.868),可临床用于无AD相关Aβ病变的认知受损者(包括SCD、MCI和非AD痴呆)和AD的鉴别诊断[9]。^{18}F-FBB在早发性AD和晚发性AD患者中的皮层摄取水平相似[10],其和^{18}F-FMM在整体皮质标准摄取值比率(standardized uptake value ratio, SUVR)的视觉评分方面,对诊断AD具有相当的效力,但^{18}F-FBB能够特异性结合NPs,因此其在鉴别诊断PCS-AD和非AD上有更高的价值[11-12]。此外,AD的^{18}F-FBB PET的阳性灰质体素数量显著多于AD-MCI和正常老年人的数量,可用于区分AD、AD-MCI和正常老年人[13]。Meta分析显示^{18}F-FMM PET与MRI诊断AD和MCI的敏感性和特异性相似,但^{18}F-FMM区别AD和MCI的特异性高于MRI[14]。综上所述,第二代Aβ示踪剂对Braak Ⅳ~Ⅴ期Aβ病变的检出率高,对Ⅲ期Aβ病变的检出率低,且无法检出早期Aβ病变。而^{18}F-FMM与MRI诊断症状AD和MCI准确性相当,特异性稍高,但第二代Aβ示踪剂与边界区白质的结合可能使图像解析变得更加复杂。

1.1.3 第三代Aβ PET示踪剂对AD和MCI的诊断价值 与其他PIB类Aβ示踪剂相比,第三代Aβ示踪剂^{18}F-NAV4694对皮层Aβ斑块的特异性结合更高,而对白质结合更低,故视觉分辨Aβ沉积的准确性更高,其阳性结果使非典型痴呆的诊断准确性提高了44%[15];体外实验在CU和AD的前额叶、下颞叶、后扣带回^{18}F-NAV4694与Aβ结合力高于PIB[16]。Centiloid标准化后,^{18}F-NAV4694在体内也与Aβ结合力较PIB更高,结合年轻者的Aβ的稳定性更高,变异性更低[17],其诊断AD敏感性更高,更适合用于诊断早发性AD。

1.2 Aβ PET对AD和MCI的预后预测价值

临床CU的NPs与整体认知评分、情景记忆、语义记忆降低相关,且与Braak分级相关性更强,而常见于Braak Ⅰ~Ⅲ级的弥散斑块(diffuse plaques, DPs)与上述认知总体表现不相关[18],提示NPs的认知预后预测价值高于DPs。^{18}F-AV45和^{11}C-PIB的整体皮层SUVR对于预测CU进展至MCI和AD的效力相当[19],预测MCI向AD转化的敏感性为0.84,特异性为0.62[8]。然而,当^{11}C-PiB的内侧颞叶SUVR与AD认知评估量表或简易精神状态评价量表(mini-mental state examination, MMSE)相结合时,其预测MCI转化为AD的特异性和准确性显著提高[19]。与^{18}F-AV45在尾核的摄取率相比,其在壳核的摄取率与认知评分的相关性更强。壳核摄取率较高的患者,具有更高的APOE4风险及AD痴呆诊断率,因此^{18}F-AV45的壳核摄取率可作为预测AD进展风险的评价指标[20]。氰基-FMM和氰基-PiB主要沉积于NPs,很少沉积于DPs,二者检测的Aβ致密斑负荷相同,且均在额叶皮层摄取(NPs和DPs)多于尾核区(DPs),故二者对CU、MCI的风险预测敏感性相当[21]。^{18}F-FMM PET与^{11}C-PIB PET相似地对AD谱系中Aβ沉积纵向评估;但Aβ沉积在AD痴呆前阶段增加更快,在临床AD以不恒定的速度增加[22],这可能使^{18}F-FMM PET衍生的复合SUVR或区域SUVR与临床痴呆评定量表评分进展无关联[23]。总之,单独Aβ PET的预后预测价值有限,临床需结合多种生物标志物、临床特征和个体化因素准确评估Aβ PET阳性MCI发展为AD的风险及预后。

1.3 Aβ PET对AD患者筛选及疗效监测价值

相比散发性AD,PIB对早发性AD的Aβ棉絮斑块的结合力低,常低估早发性AD棉絮斑块富集区的Aβ负荷,不宜单用于早发性AD的免疫治疗疗效监测[24]。Centiloid标准化后,^{18}F-NAV4694比PIB的Aβ结合力高、变异性低,抗Aβ药物的疗效监测特异性和稳定性更高[17],可能是目前抗Aβ药物的疗效监测最佳示踪剂。根据上述影像临床研究,本文总结了常用Aβ示踪剂对AD疾病谱及非AD痴呆诊断和治疗监测的优先选择,以供临床和影像医生参考,请扫文末附表1阅读。

1.4 Aβ PET对其他AD生物标志物的诊断价值

Aβ PET能够准确地复现中晚期Aβ病变,且常被用于验证其他生物标志物的诊断效力。它证实了血浆p-tau231和p-tau217能在无明显Aβ斑块病变前捕捉最早的皮层Aβ变化,可作为PCS-AD筛选试验的血浆生物标志物[25]。血浆p-tau217对Aβ PET病变的总诊断敏感性(82%)和特异性(86%)均较高,其预测Aβ PET阳性的准确性稍高于预测tau PET阳性,且在认知障碍者较CU者检测的AD病理变化有更高的预测准确性,未来可作为认知障碍者的临床诊断生物标志物[26]。此外,血浆p-tau217的两步法工作模型用于Aβ PET阳性MCI患者的风险分层,可以大大减少确认测试降低患者经济压力[27]。因此,Aβ PET和血浆p-tau217的临床应用场景可能有差别。

2　tau PET的诊疗应用价值

2.1　tau PET的诊断价值

2.1.1　第一代tau示踪剂的AD和MCI诊断价值　第一代tau示踪剂包括吡啶吲哚衍生物^{18}F-flortaucipir(^{18}F-AV1451)和^{11}C-PBB3、喹啉衍生物^{18}F-THK5317。^{18}F-AV1451于2020年被FDA批准用于体内评估PHF和NFT分布。^{18}F-AV1451在杏仁核、内嗅皮层、旁海马、梭形回及下顶叶的沉积诊断PCS-AD(93%)和AD痴呆(83%)的准确性高于结构MRI[28]。它在AD的海马及新皮层摄取率高于进行性核上性麻痹(progressive supranuclear palsy, PSP)和非AD痴呆[29]，在AD的眶额叶及中央前回的摄取率也高于额颞叶痴呆(frontotemporal lobar degeneration, FTLD)[30]，可用于AD痴呆诊断及与非AD源性tau病的鉴别诊断。但^{18}F-AV1451靶区SUVR图像定量分析只能检测到晚期AD的Braak Ⅵ病理，无法检测Braak Ⅰ-Ⅳ的病理，更不能可靠地区分AD与非AD病变[31]。相比^{18}F-AV1451，^{11}C-PBB3是广谱tau示踪剂，其能更强地与PSP的4Rtau神经胶质斑块及萎缩突起的弥散NFT结合，也可与皮克病和家族性tau病的3Rtau斑块结合[32]；^{11}C-PBB3在疑似AD和FTLD有微量和中重度这2种摄取形式，并与MMSE评分负相关，可用于非AD与AD的诊断，也可用来判断tau疾病的严重程度[33]。^{18}F-THK5317和^{18}F-AV1451诊断前驱期AD和AD痴呆均优于MRI，前者诊断前驱期AD效力最高，后者区分前驱期AD和AD痴呆更佳[34]。总之，第一代tau示踪剂可用于AD痴呆诊断及与非AD痴呆的鉴别诊断，但都有相似的脱靶结合Aβ、黑色素、脂褐素、单胺氧化酶(monoamine oxidase, MAO)[35]。

2.1.2　第二代tau示踪剂的AD和MCI诊断价值　第二代tau示踪剂^{18}F-MK6240，^{18}F-RO948临床研究应用较多，^{18}F-GTP1和^{18}F-PI2620研究报告较少。18F-MK6240在98%的受试者中显示出与Braak六分期一致的分布模式[36]。不同于^{18}F-AV1451脱靶结合纹状体和脉络丛，^{18}F-MK6240脱靶结合脑膜，且其动态SUVR是^{18}F-AV1451的两倍[37]，故诊断PCS-AD更敏感和特异。^{18}F-MK6240在UC老年人脑中呈异质性分布，其内侧颞叶沉积与AD风险因素和血浆总tau相关，双侧杏仁核-海马体的沉积与记忆负相关，新皮层广泛沉积与语言和推理受损相关，可用于PCS-AD的亚型分类[38]。^{18}F-RO948比^{18}F-AV1451在内侧颞叶沉积更高，脱靶结合颅骨和脑膜，颅内脱靶结合更低，诊断PCS-AD敏感性特异性更高[39]。^{18}F-PI2620是广谱NFT成像剂，它和^{18}F-RO948的靶区沉积相似并与Braak各期相关，但其脱靶结合血管可能干扰靶区信号定量[40]。^{18}F-PI2620比^{18}F-AV1451在体外与AD脑NFT有更高特异性结合[41]，注入体内45~75 min内能快速高信噪比成像无症状AD的NFT区(颞叶，顶叶，楔前叶和后扣带回)，其新皮层摄取率与认知受损密切相关，PCS-AD及早期AD诊断敏感性更高[42]。^{18}F-GTP1特异结合颞叶皮层聚集tau(无Aβ斑块和MAO非特异结合)，也可准确诊断AD[43]。总之，第二代tau示踪剂比第一代能更特异结合AD的NFT早期病变，脱靶结合更低，纵向跟踪稳定性更高，能辅助PCS-AD及早期AD的诊断。

2.1.2　第二代tau示踪剂的鉴别诊断价值　^{18}F-MK6240高特异结合AD各期NFT(3R/4Rtau)且白质结合低，其全脑皮层SUVR区分AD痴呆和FTLD，内侧颞叶SUVR区别Aβ阳性MCI与FTLD的准确性均达90~100%[36]。^{18}F-MK6240在新皮层的阳性沉积是高特异性AD病变，4Rtau病变的皮层基底退变(corticobasal degeneration, CBD)和PSP均无新皮层沉积，可鉴别AD-MCI和非AD-MCI[44]。^{18}F-RO948在AD的Ⅰ-Ⅳ级NFT区沉积率高于MCI及其他非AD痴呆，其诊断AD和区别非AD痴呆的效力优于MRI(全脑厚度和颞叶厚度)和脑脊液(Aβ42/p-tau181和Aβ42/Aβ40)[45]。但以颞叶meta-ROI的SUVR 1.35为通用临界值时，^{18}F-AV1451、^{18}F-RO948和^{18}F-MK6240 PET诊断AD和鉴别诊断AD与非AD痴呆的准确性相当[46]。体外^{3}H-PI2620比^{3}H-MK6240和^{3}H-RO948对CBD和PSP的前额叶4Rtau NFT特异结合更高，对PSP有最高亲和力[47]，可鉴别PSP和CBD与AD。^{18}F-PI-2620 PET/MR在AD梨状皮层的摄取率随疾病加重增加，在帕金森病(Parkinson's disease, PD)却不增加，也可早期鉴别AD和PD[48]。总之，第二代tau示踪剂能更早更准确鉴别AD与非AD tau病。

2.2　Tau PET的AD分期和进展监测价值

^{18}F-MK6240在亚皮层区的年龄相关脱靶沉积显著低于第一代tau示踪剂，且对纵向NFT量化的影响极小[49]。^{18}F-MK6240可为无症状与有症状AD提供早期和晚期tau积聚指数以便疾病分期，其在Ⅳ~Ⅵ级NFT区比在Ⅱ~Ⅳ级NFT区有更高的tau积聚速率，病理学研究证实其可用于PET Braak分

级;此外,用^{18}F-MK6240量化NFT空间分布的程度比量化SUVR在预测AD进展方面更具价值[50-51]。因此,^{18}F-MK6240可用于纵向跟踪NFT分布,评估AD疾病谱的进展。但^{18}F-MK6240的分布也受Aβ沉积的影响,故用^{18}F-MK6240PET确定NFT分期推断病程以辅助AD预后判断及发现防治时间窗时,要考虑Aβ沉积对tau扩散的大小和地形的影响[52]。以^{18}F-MK6240 PET Braak分级为框架的生物标志物模态可在活人模拟AD自然病史和监测AD严重性[53],未来有潜力应用于临床治疗监测。^{18}F-RO948沉积于Braak Ⅰ~Ⅲ期NFT区,且其在早期NFT区的沉积与对应脑区萎缩、内侧颞叶-后内侧系统功能连接减少及阶段认知下降相关,也具有AD分期和进展监测优势[54]。^{18}F-PI2620与^{18}F-MK6240、^{18}F-GTP1在Braak各期NFT病变(除Ⅱ期)有相关的沉积模式,但前二者脱靶结合脑膜,^{18}F-GTP1脱靶结合亚皮层灰质,可能影响相应区域影像解读[55]。综上,第二代tau示踪剂在AD疾病分期和进展监测优于第一代示踪剂,各tau示踪剂的靶向特点及其临床应用,请扫文末附表2阅读。

2.3 Tau PET对MCI预后的预测价值

准确预测高风险CU老年人的未来认知下降以及MCI向AD转化的风险,并有效控制相关风险因素,对于预防PCS-AD的进展至关重要。研究表明,tau PET的阳性结果及其视觉读数在预测MCI向AD痴呆转化方面的效率,均高于Aβ PET和MRI[56]。而且在CU、MCI及痴呆受试者中,tau PET的认知预后预测价值也优于Aβ PET,FDG PET及MRI检查[57-58]。在CU老年人、遗忘型MCI和痴呆患者中,tau PET基础-SUVR预测纵向MMSE下降或认知下降也优于血浆p-tau217[59-60]。综上,tau PET是AD疾病谱的最佳预后评估指标。

3 神经损伤标志物PET对AD和AD-MCI的诊断价值

3.1 ^{18}F-FDG PET对AD和AD-MCI的诊疗价值

3.1.1 ^{18}F-FDG PET对AD的诊断价值 ^{18}F-FDG PET经葡萄糖转运体转运入脑并通过星形胶质细胞和神经元共同代谢,能敏感地测定神经元活性变化,可作为神经退变性痴呆的神经代谢受损标志物。Meta分析显示,^{18}F-FDG PET在鉴别诊断痴呆亚型(尤其是AD、FTLD、路易体痴呆DLB)方面显示出高敏感性和特异性[61]。多中心研究显示^{18}F-FDG PET区别诊断AD和FTLD的效力(敏感性和准确性)高于脑脊液p-tau181[62],故^{18}F-FDG PET可用于AD痴呆诊断及对非AD痴呆的鉴别诊断。

3.1.2 ^{18}F-FDG PET对AD-MCI的诊断及预测价值 AD早期常伴有脑区域性代谢减低,AD-MCI根据^{18}F-FDG PET代谢减低最明显的部位可分为后顶颞叶低代谢型、边缘系受累为主型、外侧及额叶皮层为主型,且伴有不同症状,故^{18}F-FDG PET可结合临床表现辅助AD-MCI的亚型诊断[63]。在低龄MCI中,^{18}F-FDG PET对AD的高级神经病变的诊断特异性与PIB相似,但敏感性不如PIB[64]。DLB-MCI的后扣带回的葡萄糖代谢率高于楔前叶和楔叶,称为扣带回岛征,也可鉴别AD-MCI和DLB-MCI[65]。MCI转化AD组的内侧颞叶和后扣带回的^{18}F-FDG PET低代谢发生在MCI转化前1至8年内,并与认知下降强相关,其后扣带回、楔前叶和颞叶外侧叶的代谢减低早于MRI变化出现,提示^{18}F-FDG PET区域低代谢预测MCI转为AD的敏感性高于MRI[66]。综上,^{18}F-FDG PET可诊断低龄AD-MCI或区别非AD-MCI,也可作为MCI预后预测指标。

3.1.3 ^{18}F-FDG PET/MR对AD的诊断及预测价值 近年来,融合PET功能成像的代谢和神经递质活性信息和MRI的超清晰形态成像的PET/MR,既克服了CT的低软组织对比度和电离辐射暴露缺点,也减少了PET图像的运动伪影或部分体积影响,可提高AD诊断的准确性。FDG-PET/MR(地图集的MR衰减校正)应用在诊断AD和预测MCI转为AD时,有与PET/CT相似的诊断准确性,FDG-PET/MR(零回波时间的MR衰减校正)在SUVR的量化和痴呆分类更准确,但都导致诊断敏感性略低[67]。另外,PET/MR装置的稀缺也限制了其广泛临床应用。

3.2 突触相关蛋白PET在AD诊疗研究的应用

3.2.1 SV2A PET对早期AD和AD-CI的突触损伤评价价值 研究表明AD早期无明显Aβ斑块时即有突触受损。突触囊泡糖蛋白2A(synaptic vesicle glycoprotein 2A,SV2A)几乎分布于所有突触,^{11}C-UCB-J和^{18}F-SynVesT-1均可示踪SV2A评估突触密度,后者对SV2A的亲和力更高。^{11}C-UCB-J PET显示AD早期内侧颞叶、新皮层及海马SV2A较低,并与整体情节记忆评分正相关[68];Aβ阳性CI的海马^{18}F-SynVesT-1摄取减低与tau PET沉积和Aβ血浆标志物正相关[69]。故二者皆可检测突触受损情

况，间接评价核心病变和记忆水平辅助AD早期诊断。

3.2.2　mGluR5的AD早期诊断价值　代谢性谷氨酸亚型5受体（metabotropic glutamate subtype 5 receptors，mGluR5）调节突触传递，在Aβ寡聚体的突触毒性作用中扮演重要角色。^{18}F-FPEB PET示踪mGlu5，发现Aβ阳性遗忘型AD-MCI或轻度AD痴呆患者的海马、内嗅皮层和旁海马区^{18}F-FPEB SUVR显著下降，且海马^{18}F-FPEB SUVR与情节记忆评分和整体功能相关[70]。用^{18}F-FPEB标记mGluR5，^{11}C-UCB-J PET检测突触，发现早期认知障碍的海马mGluR5水平低，并与认知表现正相关，与tau沉积负相关[71]。说明mGluR5水平下降参与Aβ和tau病变引起的早期突触减少和认知下降，有望成为AD-MCI诊断的影像标志物。

4　神经炎症示踪剂PET的诊疗价值

4.1　小胶质细胞源性炎症标志物PET的AD-MCI诊疗价值

AD脑内神经炎症主要由小胶质细胞和星形胶质细胞激活导致。^{11}C-PBR28作为线粒体外膜转位蛋白（translocator protein，TSP）示踪剂，选择性在活化的AD小胶质细胞高表达，其沉积与AD-MCI和AD的Aβ和tau病变均正相关[72]。此外，Aβ、tau和神经炎症PET在PCS-AD和MCI也可独立预测认知[73]。TSP的新示踪剂^{11}C-ER176显示AD相关炎症与tau病变相关度高于Aβ病变，且与认知评分下降相关[74]。故^{11}C-PBR28和^{11}C-ER176均可辅助标记AD核心病变，有望成为AD进展预测的独立标志物。

4.2　星形胶质细胞源性炎症标志物PET的AD诊疗价值

星形胶质细胞代谢物柠檬酸在反应性星形胶质细胞表达升高，其可作为星形胶质细胞炎症标志物。MCI的内侧颞叶^{11}C-柠檬酸SUVR增高，其与MCI的整体和区域Aβ负荷正相关，与认知功能负相关[75]。AD患者的^{18}F-FDG低摄取率伴有内嗅皮层、海马及颞顶叶新皮层^{11}C-柠檬酸SUVR增高，二者均与患者的认知功能下降强相关[76]。这提示柠檬酸增高的反应性星形胶质细胞与神经元互作参与Aβ相关的认知下降，故^{11}C-柠檬酸SUVR有望作为AD星形胶质细胞激活的新标志物。

4.3　α-Syn PET的诊断价值

约25%~50%的AD患者脑内可见α-突触核蛋白（α-synuclein，α-Syn）沉积形成的路易小体，并且有路易小体的AD患者认知功能下降更快，提示α-Syn参与部分AD病例的快速进展。正常小胶质细胞能转运并降解α-Syn。α-Syn聚集反映小胶质细胞清运能力下降，也将加速Aβ和tau病变扩散。^{18}F-F0502B在PD动物模型及PD患者均高亲和力选择性结合脑α-Syn聚集体（不结合Aβ和tau纤维）[77]，未来有望成为含α-Syn聚集体的PD或AD的影像标志物。

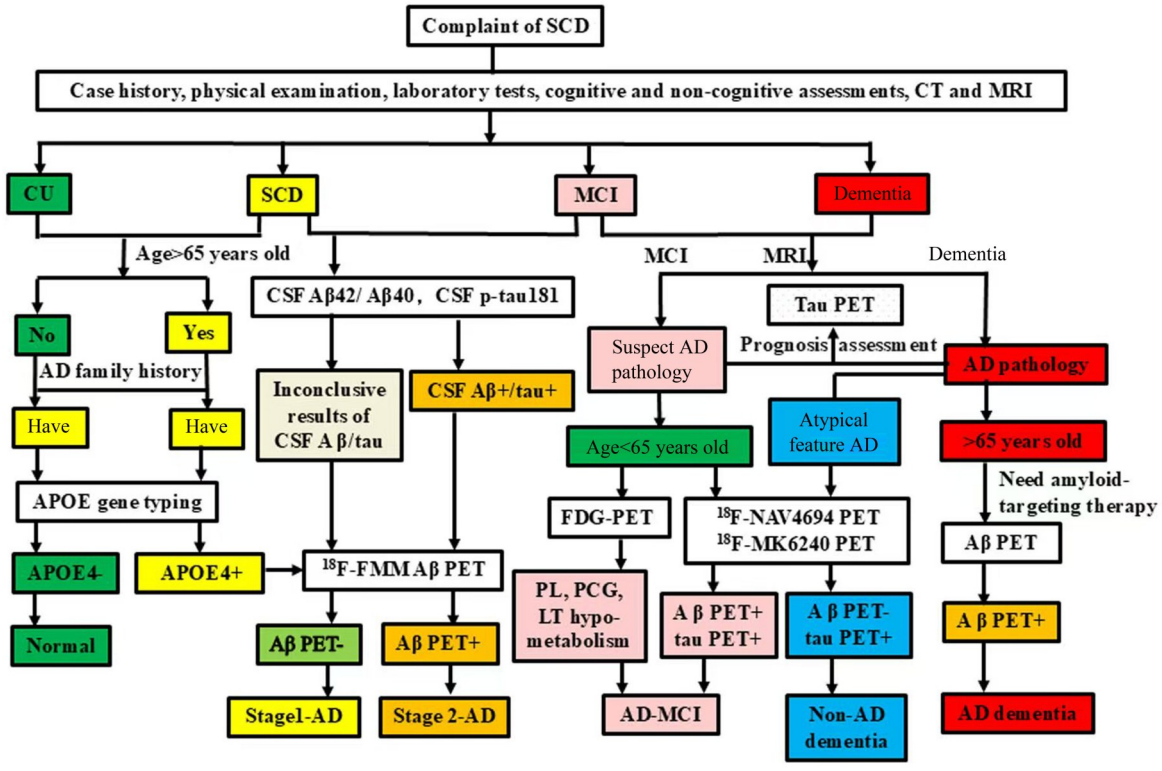
5　总结与展望

尽管PET/CT能检测AD和部分MCI的Aβ斑块，以及NFT分布与早期突触损伤，其仍然面临以下挑战：①核心病变示踪剂的非特异性结合使阳性结果的诊断特异性有限；②PET静态成像受脑血流影响，动态成像耗时且需要复杂的建模，降低其准确性或限制其应用；③PET显像的低可及性、高诊断成本、放射性接触限制了其临床广泛使用。

未来，若要将PET/CT检测广泛应用于AD-MCI的临床诊断，首先需规范PET显像流程和结果解读，以提升其诊断结果的一致性和可靠性。其次，需探索AD核心病变PET/CT的更敏感特异指标。同时，还需推进高特异Aβ示踪剂^{18}F-DRKXH1以及具有高Aβ摄取和高灰白质对比的^{18}F-Florbetazine的临床转化研究[78-79]，或加快开发新的特异性结合核心病变蛋白的安全示踪剂。最后，需制定合理的PCS-AD和AD痴呆的Aβ PET和tau PET的适用标准。最近更新的Aβ PET和tau PET的适用标准，为临床合理应用Aβ PET和tau PET提供了参考意见[80]。在此基础上，本文制定了AD早期诊断流程图（图1），以供临床选用参考。

随着AD发病率的不断升高，开发用于AD早期检测和精确监测的诊断工具显得尤为迫切。机器学习、传统神经网络和深度学习等人工智能在PET技术的应用，提高了PET图像分析的速度和准确度，实现了NFT的精准量化，从而大幅度提高AD诊断的精准性。展望未来，除了进一步发展AD PET/CT和PET/MR技术外，我们还需整合优化多种生物标志物及其效力监测，构建结合影像学和生物标志物的多模态分析诊断工具。相信日益丰富的开源AI工具，必将为人类带来可靠的AD-AI影像诊断模型，助力AD的早期诊断与精准治疗。

附表1~2
Appendix table 1-2



CT: computed tomography; MRI: magnetic resonance imaging; CU: cognitive unimpaired; SCD: subjective cognitive decline; MCI: mild cognitive impairment; CSF: cerebral spinal fluid; Aβ: β-amyloid; PET: positron emission tomographic; APOE: apolipoprotein E; PL: parietal lobe; PCG: posterior cingulate gyrus; LT: lateral temporal hypometabolism; AD: Alzheimer's disease.

图1 AD早期诊断流程图

Fig. 1 Flowchart for early diagnosis of AD

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