·标准与指南·

痴呆诊断中PET临床合理化应用中国专家共识（2021版）

中国微循环学会神经变性病专业委员会

【摘要】 痴呆是一项严重的世界性公共卫生难题，特别是随着人口老龄化的进程，其发病率逐渐升高。痴呆发病较为隐匿，以临床症状为特征的诊断框架在实际操作中效能较低，影像学标志物证据引入诊断系统使痴呆诊断的准确性大幅度提高。PET显像可以在体反映痴呆的病理学过程，是痴呆诊断的重要影像学标志物。随着国内PET设备在大型医疗机构的保有量迅速增长，临床诊疗过程中逐步开展针对痴呆患者的PET显像，但目前PET显像在痴呆中的应用证据尚待进一步完善。因此有必要在现有证据的基础上结合临床实践制定合理的临床痴呆诊断中PET应用中国专家共识，规范其在痴呆诊断中的应用。

【关键词】 痴呆； 正电子发射断层显像术； 专家共识（非*MeSH*词）； 中国

Chinese experts consensus on the optimized application of PET imaging in the diagnosis of dementia (2021 edition)

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【**Abstract**】 Dementia is a serious global public health problem, especially with the aging of the population. Its incidence will further increase. The onset of dementia is insidious, and the diagnostic framework characterized by clinical symptoms is less effective in practice. Biomarker has improved the accuracy of dementia diagnosis. PET imaging can reflect the pathological process of dementia in vivo and is an important imaging biomarker for the diagnosis of dementia. With the rapid increase in the number of PET equipment in large medical institutions, PET assessment for dementia patients has been gradually carried out during clinical diagnosis and treatment, but the current evidence of PET imaging in dementia still needs further research and improvement. So, it is necessary to plan a reasonable clinical dementia PET application guide based on the existing research evidence and the actual situation to optimize its application for the diagnosis of dementia.

【**Key words**】 Dementia; Positron-emission tomography; Expert consensus (not in *MeSH*); China
Conflicts of interest: none declared

目前，全世界约有痴呆患者5000万例，截至2050年预计达1.52亿；医疗卫生投入每年约8180亿美元，占全球生产总值的1.1%[1-3]，因此，痴呆成为严重的世界性公共卫生难题。痴呆是一种认知功能障碍综合征，可以影响记忆力、思维、定向力、理解力、计算力、学习能力、语言功能和判断力等多种高级皮质功能，从而导致日常生活活动能力明显下降。痴呆包括4种主要类型，即阿尔茨海默病、路易体痴呆（DLB）、额颞叶变性（FTLD）和血管性痴呆（VaD），其中尤以阿尔茨海默病最为常见，占全部痴呆的60%～80%[4]。

不同类型痴呆的临床表现相互重叠，故以临床特征为主要依据的诊断标准准确性较低[5-12]。随着研究的深入，生物学标志物在痴呆诊断中的作用逐渐被重视，越来越多的指南将其纳入诊断标准。2018年初，美国国家老龄化研究所-阿尔茨海默病学会（NIA-AA）开创性提出β-淀粉样蛋白（Aβ）-tau蛋白-神经退行性变[AT(N)]分期诊断系统[5]。该

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系统将生物学标志物作为是否具备阿尔茨海默病病理学特征和病情进展程度的判断标准，将疾病诊断从症状学水平提升至神经病理学层面。PET显像在生物学标志物的检测过程中扮演重要角色。PET显像是基于正电子类放射性示踪剂和扫描设备的成像手段，示踪剂注入体内后通过扫描设备显示其分布和代谢情况。由于该项技术无创性、可视化、可定量的优势，近年在脑科学领域特别是痴呆领域的研究成为热点。应用不同示踪剂的PET显像可以从多层面、多靶点反映出痴呆患者的脑功能以及核心病理改变，为痴呆的诊断提供重要依据。

一、PET显像在痴呆诊断中的应用

阿尔茨海默病的核心病理学特征为Aβ沉积形成的神经炎性斑[NPs，亦称老年斑(SPs)]和tau蛋白磷酸化形成的神经原纤维缠结(NFTs)，以及突触功能异常和神经元缺失。这一病理改变过程并非阿尔茨海默病所特有，路易体痴呆患者脑组织内亦可见异常Aβ沉积[6]，额颞叶变性患者脑组织内亦出现tau蛋白病理改变[7-9]，同时，各种类型痴呆均有突触功能异常和神经元缺失。因此，PET显像在痴呆诊断中的应用主要围绕以下两方面：(1)葡萄糖代谢的PET显像，可以反映脑组织内神经突触功能和神经元缺失情况，目前较为成熟的放射性示踪剂为^{18}F-脱氧葡萄糖(^{18}F-FDG)。(2)病理性生物学标志物的PET显像，例如Aβ、tau蛋白等，该项技术依赖于放射性示踪剂的研发，目前经美国食品与药品管理局(FDA)批准上市的Aβ示踪剂有^{18}F-florbetapir、^{18}F-flutemetamol和^{18}F-florbetaben，而tau蛋白示踪剂^{18}F-flortaucipir(AV-1451)于2020年批准上市。

1.^{18}F-FDG PET显像　^{18}F-FDG PET通过测定脑组织内与谷氨酸能突触和星形胶质细胞活动相关的局部葡萄糖消耗量，以评估脑代谢情况。代谢较低提示神经细胞功能障碍，从而为神经退行性变提供证据；低代谢的分布模式决定认知功能障碍类型和严重程度，故^{18}F-FDG PET在痴呆的诊断与鉴别诊断中具有重要意义[10]。有研究显示，阿尔茨海默病患者顶叶、颞叶和后扣带回葡萄糖代谢率特征性降低，可资与正常对照者区分(灵敏度为96%，特异度为100%)[11]。与病理学检查这一“金标准”相比，^{18}F-FDG PET诊断阿尔茨海默病的灵敏度为93.81%，特异度为73.17%[12]。亦有研究显示，不典型阿尔茨海默病也具有特征性低代谢区[13]。轻度认知损害(MCI)阶段，^{18}F-FDG PET可较MRI更早显现出神经退行性变的特征性模式[14-16]，随着病情进展，特定区域葡萄糖代谢率可呈现特征性和渐进性降低，提示^{18}F-FDG PET可以潜在预测轻度认知损害向阿尔茨海默病的转变[14,17-19]。路易体痴呆患者^{18}F-FDG PET显像特征性表现为广泛的外侧额叶和颞顶叶低代谢，同时具备有别于阿尔茨海默病的枕叶低代谢以及中扣带回和后扣带回葡萄糖代谢率相对保留，称为“枕叶低代谢”和“扣带回岛征”，这两项特征具有重要的鉴别诊断意义[20-23]。采用优化的半定量^{18}F-FDG PET显像进行分析后，路易体痴呆的诊断准确度高达91.67%[24]。额颞叶变性患者^{18}F-FDG PET的典型征象为额颞叶低代谢，可有效区分行为异常型额颞叶痴呆(bvFTD)与阿尔茨海默病(灵敏度89.29%，特异度78.13%)以及行为异常型额颞叶痴呆与正常人群(灵敏度79.31%，特异度100%)[25-26]；^{18}F-FDG PET对原发性进行性失语(PPA)的鉴别诊断灵敏度为60%～91.67%，特异度为94.44%～100%[27-28]。血管性痴呆的^{18}F-FDG PET可见多个局灶性皮质和皮质下低代谢区且有明显异质性，与阿尔茨海默病特征性低代谢分布模式明显不同，有助于二者鉴别诊断[29]。对临床诊断困难的轻度认知损害和痴呆患者，^{18}F-FDG PET显像可显著提高临床诊断准确性，阿尔茨海默病诊断准确率自70%增至90%，额颞叶变性自85%增至94%[30]。基于上述研究结果，各项国际指南对^{18}F-FDG PET作为痴呆诊断的影像学标志物予以正面推荐意见：2007年，由国际工作组(IWG)和NIA-AA联合制定的《研究用阿尔茨海默病诊断指南》首次将^{18}F-FDG PET作为阿尔茨海默病诊断的影像学标志物[31]；2014年的《研究用阿尔茨海默病诊断指南更新版》将^{18}F-FDG PET确认为反映阿尔茨海默病进程的影像学标志物[32]；2018年发布的《NIA-AA研究框架：阿尔茨海默病生物学定义指南》中，^{18}F-FDG PET作为阿尔茨海默病诊断影像学标志物的地位稳固提高[5]。2017年，《路易体痴呆诊断与治疗指南》推荐，^{18}F-FDG PET显示的“后扣带回岛征”作为路易体痴呆诊断的支持性影像学标志物[33]。2011年修订的《行为异常型额颞叶痴呆指南》将^{18}F-FDG PET显示的额叶、前颞叶低代谢作为诊断的影像学标志物之一[34]。同年，《原发性进行性失语分类及其变异指南》推荐，左侧后额叶-岛叶、左侧前颞叶、左侧外侧裂周围后部或者顶叶低代谢分别作为非流利性变异型原发性进行性失语(nfvPPA)、语义变异型原

发性进行性失语(svPPA)以及Logopenic型原发性进行性失语(LPA)诊断的支持性影像学标志物[35]。2020年,美国放射学会(ACR)制定的《痴呆适宜性应用指南》推荐,在阿尔茨海默病、额颞叶变性和路易体痴呆的诊断中行^{18}F-FDG PET显像是"可能合适的",但是其放射线暴露水平稍高(4级放射,10~30 mSv)[36]。尽管^{18}F-FDG PET在痴呆诊断中具有重要作用,但其所代表的神经退行性变仍无法反映疾病的神经病理学信息,代谢改变多为核心病理改变的下游表现,因此其在AT(N)分期诊断系统中的地位低于Aβ和tau蛋白标志物。

2. Aβ-PET显像 阿尔茨海默病的病理改变最先为β-淀粉样前体蛋白(APP)加工异常导致Aβ病理性沉积,这一过程在临床症状出现前数年即已开始[37]。故AT(N)分期诊断系统中,Aβ被确定为阿尔茨海默病病理改变的核心标志物,也是诊断的必要条件[5]。研究显示,脑脊液$A\beta_{42}$降低以及Aβ-PET显像提示放射性配体脑组织内高滞留率[32,38]均间接和直接反映脑组织内Aβ沉积情况。但与PET相比,脑脊液Aβ测定无法显示Aβ病理改变的程度和范围,限制其临床应用。早期Aβ-PET显像常用示踪剂为^{11}C-匹兹堡复合物B(^{11}C-PIB),但是由于^{11}C半衰期较短(20分钟),其临床应用受到限制;^{18}F标记的示踪剂半衰期为110分钟,业已在科研和临床获得广泛认可。目前,经FDA批准上市的3种Aβ放射性示踪剂均在病理学研究中发现可与脑组织内Aβ特异性结合,示踪剂与Aβ的结合程度与尸检Aβ负荷显著相关,联合应用3种示踪剂的敏感性和特异性均较高[39-42]。有文献报道,在未行脑脊液Aβ测定和^{18}F-FDG PET显像的情况下,辅助应用Aβ-PET后痴呆修正诊断率达31.26%[43],早发型痴呆修正诊断率达41.46%[44]。早期多项Aβ-PET显像研究证实,Aβ-PET显像可以有效区分阿尔茨海默病患者与正常对照者[45-46]。与尸检病理学结果的对照研究显示,Aβ-PET高滞留率区域与Aβ斑块沉积区域相匹配[47-48]。研究显示,阿尔茨海默病患者随访2年后^{11}C-PIB滞留率与基线无明显差异[49],表明阿尔茨海默病初期Aβ沉积即已达到较高的平台期,与病理学研究结果相符,因此,Aβ-PET不宜用于阿尔茨海默病分期和预测预后。后续关于轻度认知损害向阿尔茨海默病进展的研究显示,^{18}F-florbetapir[50]和^{18}F-flutemetamol[51]预测轻度认知损害向痴呆进展的准确性逐年下降。晚近研究结果显示,Aβ-PET的预测价值稍低于^{18}F-FDG PET[17]。因此尚不推荐Aβ-PET用于轻度认知损害转归的预测。Aβ-PET显像可以有效显示Aβ的病理学特征,但多种痴呆类型均存在这一病理过程的重叠,因此Aβ-PET鉴别诊断的效能有所下降。针对路易体痴呆的Aβ-PET显像研究显示,路易体痴呆患者^{11}C-PIB滞留率较帕金森病或帕金森病痴呆(PDD)患者升高,较阿尔茨海默病降低[52]。Aβ-PET显像虽可鉴别路易体痴呆与帕金森病或帕金森病痴呆,且其^{11}C-PIB滞留率降低可反映认知功能减退速度[6],但仍无法有效区分路易体痴呆与阿尔茨海默病[53]。后续Aβ-PET显像与病理学结果的对比研究显示,低^{11}C-PIB摄取率模式可以区分路易体痴呆与阿尔茨海默病,但相关证据仍有限[54]。额颞叶变性患者脑组织存在类似阿尔茨海默病的tau蛋白病理改变[8-9],但并不存在Aβ病理改变,故Aβ-PET显像阳性可以排除额颞叶变性[41,55-58]。国内一项纳入1193例认知功能障碍患者的多中心研究显示,阿尔茨海默病和额颞叶变性患者Aβ-PET阳性率分别为86.77%(833/960)和5.56%(2/36),显示出良好的鉴别诊断能力[57]。得益于Aβ在阿尔茨海默病诊断体系中的重要地位以及PET显像示踪剂的发展,2020年ACR《痴呆适宜性应用指南》推荐,阿尔茨海默病诊断中应用Aβ-PET显像是"可能合适的",放射线暴露水平为3级放射(1~10 mSv),但对路易体痴呆的诊断价值十分有限[36]。2017年的《路易体痴呆诊断与治疗指南》并未推荐Aβ-PET显像作为诊断标志物[33]。2014年的《研究用阿尔茨海默病诊断指南更新版》[32]以及2018年的《NIA-AA研究框架:阿尔茨海默病生物学定义指南》[5]均将Aβ-PET显像作为阿尔茨海默病诊断的重要影像学标志物。2011年修订的《行为异常型额颞叶痴呆指南》推荐,将Aβ-PET显像呈阴性作为排除阿尔茨海默病的标准[34]。2013年,美国核医学与分子影像学会(SNMMI)以及美国阿尔茨海默病学会(AA)联合制定的《Aβ-PET适宜性应用指南》限定轻度认知损害患者行Aβ-PET显像的范围为"症状正在进行且原因不明"[59]。

3. tau-PET显像 病理学研究显示,阿尔茨海默病患者Aβ沉积数年后可出现tau蛋白超磷酸化致神经原纤维缠结,进而出现微管稳定性下降、神经元功能障碍[60]。后续研究发现,阿尔茨海默病的临床特征由脑组织内tau蛋白病理改变部位和分布决定,tau蛋白的异常负荷可以准确预测疾病严重程度

和认知功能下降速度[61-62]。此外，tau蛋白表达异常是除阿尔茨海默病外的其他类型痴呆如额颞叶变性、进行性核上性麻痹（PSP）和路易体痴呆等的核心病理生理学机制，并被认为是病情进展的关键驱动因素。2020年，FDA批准上市首个tau-PET示踪剂^{18}F-flortaucipir[63]，在体研究业已证实其与tau蛋白病理学过程一致的结合模式[64-65]，并显示出与认知功能下降[66]和脑脊液tau蛋白表达变化的强相关性[67-68]。目前，大多数tau-PET显像研究集中于轻度认知损害和阿尔茨海默病[65,69-79]，阿尔茨海默病患者主要表现为颞顶叶皮质tau蛋白沉积增加，可资与正常对照者相区分[69,72,76,79]。*MAPT*基因突变在额颞叶变性患者中最常见，部分患者颞极、海马和颞下回、额叶^{18}F-flortaucipir滞留明显[80-81]。路易体痴呆患者则颞顶叶皮质和楔前叶^{18}F-flortaucipir滞留率增加[82]。虽然tau-PET显像在痴呆早期诊断与鉴别诊断方面具有巨大潜力，但是由于tau蛋白位于细胞内，体内水平较低，具有不同的分子构像，因此其放射性配体的研发远落后于Aβ示踪剂。第一代tau-PET示踪剂主要为^{18}F-flortaucipir、^{11}C-PBB3、^{18}F-THK535，显示出对阿尔茨海默病特异性3R/4R tau蛋白异构体的高亲和力，但是与单胺氧化酶A/B（MAO-A/B）、神经黑色素等脱靶结合，使其应用受限[83-86]。第二代tau-PET示踪剂如^{18}F-RO6958948、^{18}F-GTP1、^{18}F-PI2620、^{18}F-MK6240、^{18}F-PM-PBB3等，在高亲和力、选择性和特异性的基础上可以有效减少脱靶结合[83-85]。^{18}F-PI2620不仅与阿尔茨海默病特异性3R/4R tau蛋白异构体结合，还与进行性核上性麻痹和（或）皮质基底节变性（CBD）特异性4R tau蛋白异构体相结合[87]。^{18}F-PM-PBB3可以有效识别阿尔茨海默病和额颞叶痴呆患者脑组织内tau蛋白分布，其摄取率增加与皮质低代谢区和认知功能下降密切相关[81,88]。尽管第二代tau-PET示踪剂的研究数据令人鼓舞，但其在科研与临床中的应用价值研究上处于初步阶段，尚待更大规模的临床试验加以验证。

4.其他示踪剂PET显像　神经退行性变进展过程中常伴随神经元突触密度降低，故神经元突触密度有望成为痴呆诊断的影像学标志物。突触囊泡蛋白2A（SV2A）-PET示踪剂的研发首次实现对在体神经元突触密度的检测[89-90]。晚近研发的新型示踪剂^{11}C-UCB-J在临床前研究中显示出良好的药代动力学和定量特性[89,91]。^{18}F-MNI 1126也在非人类灵长类动物体内显示出良好特性[92]。多巴胺能神经系统功能评估在路易体痴呆与阿尔茨海默病的鉴别诊断中作用重大，纹状体^{18}F-fluorodopa再摄取减少可资鉴别路易体痴呆与阿尔茨海默病，并具有较高的灵敏度（86.67%）和特异度（100%）[93]；多巴胺转运体（DAT）-SPECT鉴别诊断二者的灵敏度为0.87，特异度为0.92[94]，基于SPECT的明显优势，目前国际上均将DAT-SPECT作为路易体相关疾病诊断的生物学标志物。然而尚未开发出针对路易体相关疾病病理改变过程中α-突触核蛋白（α-Syn）的有效PET示踪剂[95]。脑组织炎症反应参与痴呆的进程，2015年的一项系统评价显示，大多数阿尔茨海默病患者存在至少1个神经解剖区域的神经炎症反应增强[96]；一项晚近研究亦显示，轻度认知损害和阿尔茨海默病进展过程中神经炎症反应增强[97]。神经炎症反应由小胶质细胞和星形胶质细胞介导，小胶质细胞内相对分子质量为18×10^3的转运蛋白TSPO表达上调[98-100]，故推测TSPO是PET研究的另一靶点。第一代TSPO示踪剂^{11}C-PK11195生物利用率较低、非特异性结合较高，临床应用受限[98]。第二代示踪剂如^{11}C-PBR28、^{18}F-DPA714、^{18}F-FEPPA、^{11}C-DAA1106、^{18}F-PBR06、^{18}F-PBR111等，生物利用率和信噪比明显提高，但易受*TSPO*基因多态性的影响，导致不同受试者之间结果一致性较差[98]。第三代示踪剂^{18}F-GE180[101]、^{11}C-ER176[102]不受基因多态性的影响，拥有更广泛的应用前景。然而神经炎症反应是高度复杂的过程，目前尚未完全了解其过程，TSPO等神经炎症反应标志物是否可以作为痴呆诊断的生物学标志物尚待进一步研究。

二、痴呆诊断中PET显像临床应用推荐

由此可见，PET显像可以显示出痴呆的核心病理改变，且敏感性和特异性均较高。在生物学标志物有效性分析路径图中，^{18}F-FDG PET已完成有效性分析、临床有效性和实用性验证；Aβ-PET已完成有效性分析、临床有效性验证[10]，提示PET显像有助于痴呆的临床诊断与鉴别诊断，特别是在现有以临床特征为基础的诊断框架下诊断困难的病例。然而，目前关于痴呆患者PET显像的临床应用经验仍十分有限，已发表的数据主要来自高度选择性、具有典型临床特征的患者，大多数研究集中于技术可行性和疾病机制的探索，并非评估其在痴呆诊断中的价值；并且，不同示踪剂的特性仍存在不足和缺陷。基于此，本共识专家组在系统回顾痴呆诊断中

PET显像临床应用的大量文献后，参考国际指南，并结合医学伦理、医疗费用、放射线暴露风险等实际问题后提出以下一致性意见：(1)本共识力求从神经病理学角度为痴呆的诊断提供生物学标志物的支持，在诊断困难情况下为临床决策提供帮助，不与现行的痴呆诊断指南相冲突。(2)认知功能障碍患者行PET显像前需完成详细的临床病史采集、神经心理学测验和结构性影像学检查。(3)根据目前证据，^{18}F-FDG PET和Aβ-PET是痴呆诊断中有效性得到证实的影像学标志物检测手段，因此本共识基于这两种的临床应用予以推荐。(4)考虑到昂贵的检测费用、放射线暴露的风险等问题，这两项检测方法仅在诊断困难的情况下权衡利弊后应用，并不适用于临床诊断明确、体检等情况。(5)^{18}F-FDG PET、Aβ-PET优先顺序的选择应根据各自特点和实际情况而定，如^{18}F-FDG PET在病情分级、轻度认知损害转归预测、检测费用中具有优势；Aβ-PET则在确认Aβ病理过程以及早发型痴呆的鉴别诊断中具有优势。

推荐使用的情况：

1.持续性或进行性原因不明的轻度认知损害患者首选^{18}F-FDG PET显像，如低代谢模式无特异性可继续完善Aβ-PET显像。

2.有明确认知功能下降，考虑诊断为“可能的阿尔茨海默病”，但临床表现不典型、可能有混合病因时，推荐行Aβ-PET显像(或脑脊液Aβ测定)，如果Aβ-PET呈阴性，可继续完善^{18}F-FDG PET显像。

3.临床鉴别诊断困难的痴呆患者首选^{18}F-FDG PET显像，例如低代谢模式无特异性可以继续完善Aβ-PET显像。

4.早发型(发病年龄＜65岁)痴呆患者推荐Aβ-PET显像。

不推荐使用的情况：

1.晚期严重痴呆。

2.临床症状和病程符合典型阿尔茨海默病临床诊断。

3.无症状性患者[包括有痴呆、载脂蛋白Eε4(*ApoEε4*)等位基因阳性家族史]的发病前诊断。

4.有认知功能障碍主诉但未经临床确认。

5.对痴呆治疗效果的预测。

6.非医疗目的(如入职体检、保险筛选等)。

7.无法预测PET结果对患者产生何种心理和社会影响。

综上所述，PET显像作为痴呆领域具有广阔前景的诊断技术在临床的应用仍处于探索阶段，随着研究的不断深入，^{18}F-FDG PET和Aβ-PET等在临床的实际应用将进一步得到验证，以PET显像作为重要生物学标志物所构建的临床痴呆诊断框架也将日趋合理。

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