·阿尔茨海默病神经影像学研究·

^{18}F-FDG PET显像鉴别阿尔茨海默病与额颞叶痴呆临床价值

崔瑞雪　牛娜　张颖　袁晶　李方

【摘要】 **目的**　探讨^{18}F-FDG PET显像在阿尔茨海默病与额颞叶痴呆鉴别诊断中的应用价值。**方法**　对临床明确诊断的阿尔茨海默病(20例)和行为异常型额颞叶痴呆(20例)患者的^{18}F-FDG PET显像资料进行回顾,分析两组患者皮质代谢降低脑区间的差异。**结果**　视觉分析显示,两组患者均表现为皮质代谢降低,阿尔茨海默病患者以双侧颞顶叶和后扣带回代谢降低明显,以及部分额叶皮质代谢降低,而基底节和丘脑不受累,18/20患者双侧大脑半球皮质代谢降低范围和程度基本对称;额颞叶痴呆患者额叶和前颞叶皮质代谢均降低,其中11例同时伴部分顶叶皮质和基底节、丘脑等皮质下核团不同程度降低,16/20患者双侧大脑半球代谢降低程度和范围明显不对称,4例以右侧为主、12例以左侧为主。**结论**　由于^{18}F-FDG PET显像所显示的阿尔茨海默病和额颞叶痴呆患者之皮质代谢降低图型不同,故具有较好的鉴别诊断价值。

【关键词】 阿尔茨海默病;　痴呆;　正电子发射断层显像术

Value of ^{18}F-FDG PET in differentiating Alzheimer´s disease with frontotemporal dementia

CUI Rui-xue[1], NIU Na[1], ZHANG Ying[1], YUAN Jing[2], LI Fang[1]

[1]Department of Nuclear Medicine, [2]Department of Neurology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China

Corresponding author: CUI Rui-xue (Email: mmdhmm@126.com)

【**Abstract**】 **Objective**　To delineate the pattern of reduction of cerebral glucose metabolism in patients with Alzheimer´s disease (AD) and frontotemporal dementia (FTD) and investigate the value of ^{18}F-FDG PET in the differential diagnosis. **Methods**　Twenty patients with FTD (behavioral variant) and 20 AD patients underwent ^{18}F-FDG PET scanning. All the images were compared with that from 20 healthy age-matched control subjects on a voxel-based analysis (VBA) using SPM5. Visual analyses of ^{18}F-FDG PET were performed by 2 independent nuclear medicine specialists who were blinded to the clinical background. **Results**　1) The PET scans of all the patients in 2 groups presented impairment of cortical metabolism. 2) Subjects with AD showed hypometabolism in the bilateral temporoparietal association cortex and posterior cingulate cortex, and hypometabolim in part of bilateral frontal lobes was observed in patients with progression. The metabolic activity was relatively kept in the primary motor-sensor cortex, occipital lobes and subcortical structures (basal ganglia and thalamus). The asymmetric hemispheric hypometabolic involvement was rare and observed in only 2 of 20 cases. 3) Subjects with FTD showed a significant hypometabolism of the frontal lobes and anterior temporal lobes, accompanied by mild to moderate reductions in glucose metabolism in parietal cortices and subcortical structures. The asymmetric hemispheric hypometabolic involvement was commonly observed in 16 of 20 cases with right-dominant type in 4 of 16 cases and left-dominant type in 12 cases. **Conclusions**　^{18}F-FDG PET is a reliable diagnostic test in distinguishing FTD from AD due to the sharp contrast pattern of cerebral glucose hypometabolism.

【**Key words**】 Alzheimer disease;　Dementia;　Positron-emission tomography

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作者单位:100730 中国医学科学院 北京协和医学院 北京协和医院核医学科(崔瑞雪、牛娜、张颖、李方),神经科(袁晶)

通讯作者:崔瑞雪(Email:mmdhmm@126.com)

阿尔茨海默病(AD)和额颞叶痴呆(FTD)是神经变性疾病引起的主要痴呆类型[1-2]。临床主要根据患者症状与体征,以及疾病进程进行诊断。由于这两种痴呆类型的临床表现存在交叉,二者鉴别诊断有时十分困难。近年来,针对阿尔茨海默病病理学基础的药物研究取得了一定成果,不断有新药问世,但有些药物,如胆碱酯酶抑制药不仅对额颞叶痴呆无效,甚至可能会加重病情[3-4]。基于新药临床试验具有针对性的研究对象、药效评价及临床正确治疗的要求,两种痴呆类型的鉴别诊断即显得尤为重要,目前的研究热点在于寻找能够早期诊断和鉴别诊断的生物学标志。据文献报道,^{18}F-FDG PET显像在不同类型痴呆病程之早期即可表现出不同特定脑区的代谢变化[3,5-9],是目前较具希望的影像学标志之一。国内关于PET显像对痴呆诊断的应用和临床研究刚刚起步,笔者拟通过对北京协和医院临床诊断为阿尔茨海默病和额颞叶痴呆患者的^{18}F-FDG PET显像资料进行回顾分析,探讨阿尔茨海默病和额颞叶痴呆两种痴呆类型脑代谢图型变化特点及差异性,以评价^{18}F-FDG PET显像诊断与鉴别诊断价值。

资料与方法

一、研究对象

1. 痴呆组 选择2008年1月–2010年10月在我院就诊并根据临床症状和随访结果(28~60个月)最终临床诊断的阿尔茨海默病和额颞叶痴呆患者各20例,均行^{18}F-FDG PET显像,其中5例在随访过程中复查PET显像。所有患者均行头部常规MRI检查,以排除其他中枢神经系统疾病和脑血管病。(1)阿尔茨海默病组:诊断符合美国国立神经病学、语言障碍和卒中研究所-阿尔茨海默病及相关疾病协会(NINCDS-ADRDA)标准[10]。发病距PET显像时间为1~8年,平均(4.80±2.06)年;简易智能状态检查量表(MMSE)评分11~24分,平均(18.01±5.65)分。(2)额颞叶痴呆组:诊断符合1998年Neary等[11]提出的标准。发病距PET显像时间为1~5年,平均(3.45±1.37)年;MMSE评分11~24分,平均(17.28±6.15)分。

2. 正常对照组(对照组) 选择同期在我院进行体格检查、性别和年龄与痴呆组相匹配、且无神经精神疾病的健康志愿者共20例,获得知情同意后进行^{18}F-FDG PET显像。

对各组受试者性别、年龄等社会人口学特征进行比较,结果显示组间差异无统计学意义(均$P>0.05$,表1),具有可比性。

二、研究方法

1. ^{18}F-FDG PET显像 (1)主要药品来源:显像剂^{18}F-FDG由北京协和医院合成,放射化学纯度和标记率>95%。^{18}F由美国CTI公司RDS111型回旋加速器生产。(2)仪器与设备:采用德国Siemens公司生产的Biograph 64 PET/CT扫描仪。(3)检查方法:受试者禁食6 h以上,于安静、避光环境经静脉注射^{18}F-FDG 296 MBq,45 min后行PET显像。先进行头部CT扫描,用于PET数据的衰减校正,再进行10 min的三维发射断层扫描,PET数据处理采用有序子集最大似然法(OSEM)重建,分别获得横断面、冠状位和矢状位图像。

2. SPM数据处理与统计分析 (1)数据处理:所有图像数据的预处理均由SPM5统计软件完成。在

表1 各组受试者社会人口学特征的比较*

Table 1. Characteristics of subjects in 3 groups*

Group	N	Sex case (%)		Age ($\bar{x}\pm s$, year)	Time of imaging from onset ($\bar{x}\pm s$, year)	MMSE ($\bar{x}\pm s$, score)
		Male	Female			
Control	20	8 (8/20)	12 (12/20)	63.02±7.35		
AD	20	7 (7/20)	13 (13/20)	65.70±7.85	4.80±2.06	18.01±5.65
FTD	20	9 (9/20)	11 (11/20)	61.21±6.78	3.45±1.37	17.28±6.15
Statistical value		0.417		3.049	258.000	230.500
P value		0.812		0.218	0.116	0.414

*χ^2 test for comparison of sex, nonparametric Kruskal-Wallis *H* test for comparison of age, and nonparametric rank sum test for comparison of time of imaging from onset and MMSE。AD, Alzheimer's disease, 阿尔茨海默病;FTD, frontotemporal dementia, 额颞叶痴呆;MMSE, Mini-Mental State Examination, 简易智能状态检查量表

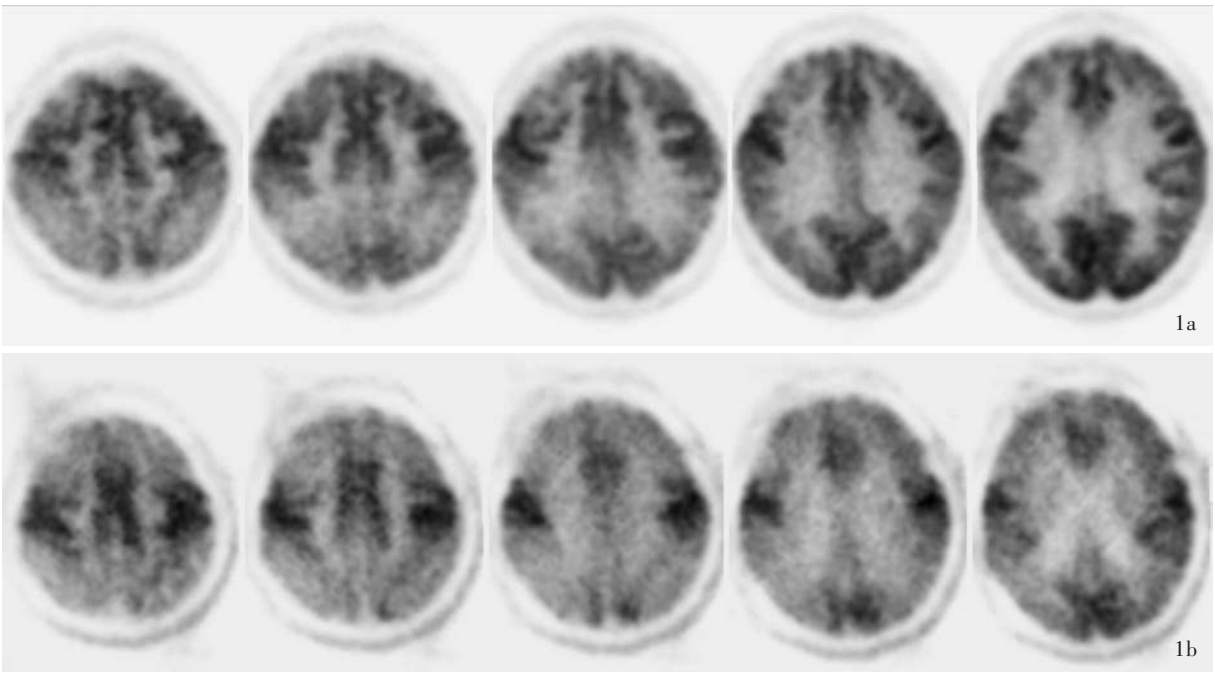


图1　女性患者，57岁，临床诊断为阿尔茨海默病。^{18}F-FDG PET显像所见　1a　首次显像时MMSE评分21分，连续横断面扫描，双侧颞顶叶皮质对称性代谢降低，额叶背外侧部分皮质代谢降低　1b　30个月后再次显像时MMSE评分17分，连续横断面扫描，双侧颞顶叶皮质对称性代谢降低程度加重，且额叶皮质代谢降低程度和范围加重

Figure 1　Serial ^{18}F-FDG PET scans in a 57-year-old female patient with AD. Hypometabolism was presented in bilateral temporoparietal lobes and partial dorsolateral frontal lobe on serial axial frames of the first ^{18}F-FDG PET imaging with MMSE 21 (Panel 1a). After 30 months, the extent of hypometabolic regions became larger both in bilateral temporoparietal lobes and frontal lobe on the second ^{18}F-FDG PET with MMSE 17 (Panel 1b).

Matlab Version 7.0平台上，应用SPM5软件对PET图像按照加拿大蒙特利尔神经病学研究所（MNI）脑图谱进行标准化处理，转化为标准解剖空间图像，再以10 mm×10 mm×10 mm半高全宽（FWHM）对标准化后的图像进行平滑处理，提高统计分析前的图像信噪比（SNR），并获得目标分析图像。（2）统计分析：对各组受试者的PET图像进行SPM统计分析（组间t检验），检验水准为未校正$P \leqslant 0.05$，获得具有统计学意义的像素点空间坐标，应用xjView软件显示代谢异常像素点对应的功能脑区，并投射到三维标准模型上（在预处理数据时，行视觉分析，即将右侧降低为主的病例图像进行左右镜像翻转，以体现病变皮质代谢降低的不对称性）。对同一例患者不同病程中的两次^{18}F-FDG PET显像变化进行定量分析，采用SPM软件将两次图像标准化后，在像素水平进行图像相减，计算各脑区的功能降低情况。

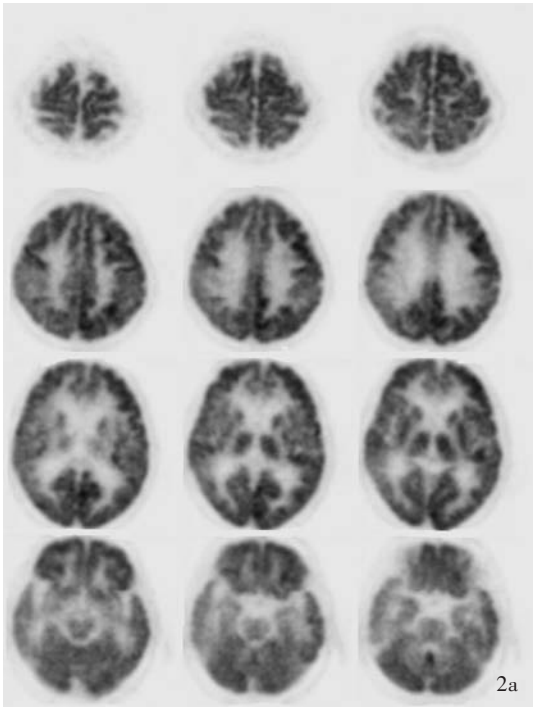
结　果

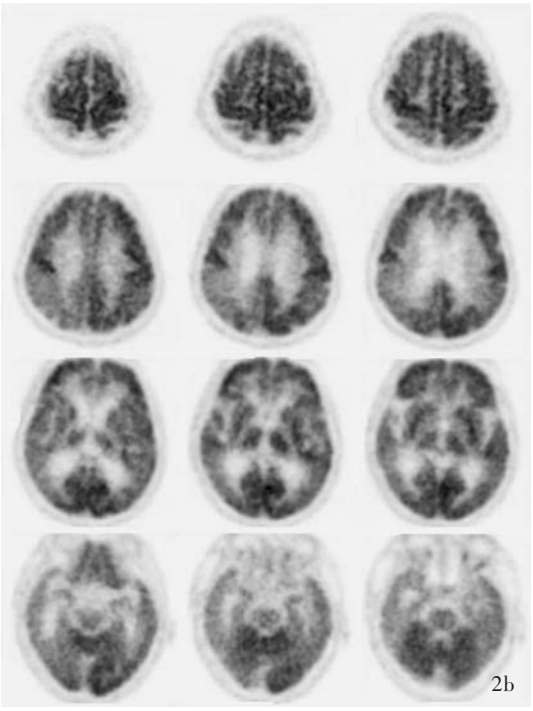
一、阿尔茨海默病视觉分析

阿尔茨海默病组患者^{18}F-FDG PET显像可见皮质代谢不同程度降低，皮质代谢降低程度和范围与病程相关，随着病情进展，代谢降低程度和范围呈渐进性加重（图1，2）。于病程早期即可见颞顶叶皮质和后扣带回代谢降低，随着病情进展，部分双侧额叶皮质代谢亦降低，病情严重时双侧额顶颞叶皮质和后扣带回代谢明显降低，但基本感觉运动皮质和枕叶视皮质代谢活性相对保留，基底节、丘脑代谢降低不明显。大部分患者（18/20）双侧大脑半球代谢水平降低程度和范围基本对称（图1），仅少数（2/20）皮质代谢水平降低以单侧大脑后部显著，其中1例随访2.50年时皮质代谢进一步降低，且双侧大脑半球降低程度和范围趋于对称（图2）。

二、额颞叶痴呆视觉分析

额颞叶痴呆组患者^{18}F-FDG PET显像表现为明显的额叶和前颞叶皮质代谢降低，其中病程较长者11例，部分顶叶皮质代谢亦降低，但降低程度和范围仍以额叶最为显著。有16/20的患者双侧大脑半球代谢降低程度和范围明显不对称，4例以右侧大脑半球为主、12例则以左侧大脑半球为主（图3）。有14例患者同侧皮质下结构（基底节、丘脑）代谢降





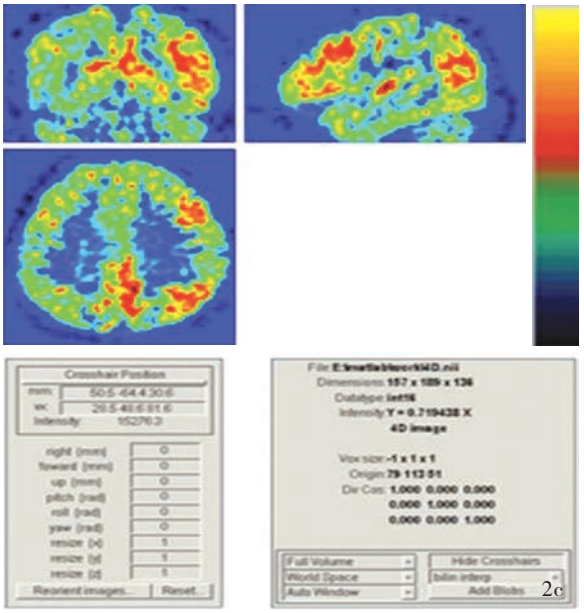


图2 女性患者，72岁，临床诊断为阿尔茨海默病。^{18}F-FDG PET显像所见 2a 首次检查连续横断面扫描显示，双侧颞顶叶皮质代谢降低，以右侧顶叶、左侧颞叶内侧更为显著；右侧额叶轻度降低，左侧额叶不明显 2b 32个月后再次检查，连续横断面扫描皮质代谢降低程度和范围明显加重，以左侧大脑半球为主，但双侧趋于对称 2c SPM分析显示，第2次显像减第1次显像，皮质代谢水平呈弥漫性降低（左侧大脑半球红色区域为代谢降低明显区域）

Figure 2 Serial ^{18}F-FDG PET scans in a 72-year-old female patient with AD. Hypometabolism was presented in bilateral temporoparietal lobes but predominantly in right parietal lobe and left medial temporal lobe, mildly in right frontal lobe but not obvious in left frontal lobe on serial axial frames of the first ^{18}F-FDG PET imaging (Panel 2a). After 32 months, the extent of hypometabolic regions became larger and decreased uptake of ^{18}F-FDG became severe, especially in left hemisphere, thus the hypometabolism became more symmetric than before (Panel 2b). The result of the second PET scan minus the first PET scan based on the voxel level by SPM analysis showed the cortical region with diffusively decreased uptake of ^{18}F-FDG (red areas at left hemisphere indicate the most obvious hypometabolic region, Panel 2c).

低，甚至对侧小脑皮质也呈现代谢降低。

三、两种痴呆类型PET显像的比较

采用SPM软件进行像素水平的组间t检验，将有统计学意义的低代谢脑区投射至标准正常大脑（图4）。与对照组相比，额颞叶痴呆组患者代谢降低脑区主要集中在额叶和前颞叶皮质，顶叶背外侧皮质呈轻度局灶性减低，低代谢以前部脑皮质为主，且双侧大脑半球代谢降低程度与范围不对称；阿尔茨海默病组患者代谢降低脑区以颞顶叶皮质为主，额叶皮质呈局灶性轻度降低，病变主要集中在大脑后部，且双侧大脑半球同时受累、大致对称，基本感觉运动皮质、枕叶视皮质基本不受累。

讨 论

阿尔茨海默病为临床常见的老年期痴呆[1]，其病理学基础为神经元内神经原纤维缠结（NFTs）形成，以及神经元外神经炎性斑[NPs，又称老年斑（SPs）]和β-淀粉样蛋白（Aβ）沉积，伴随神经元和突

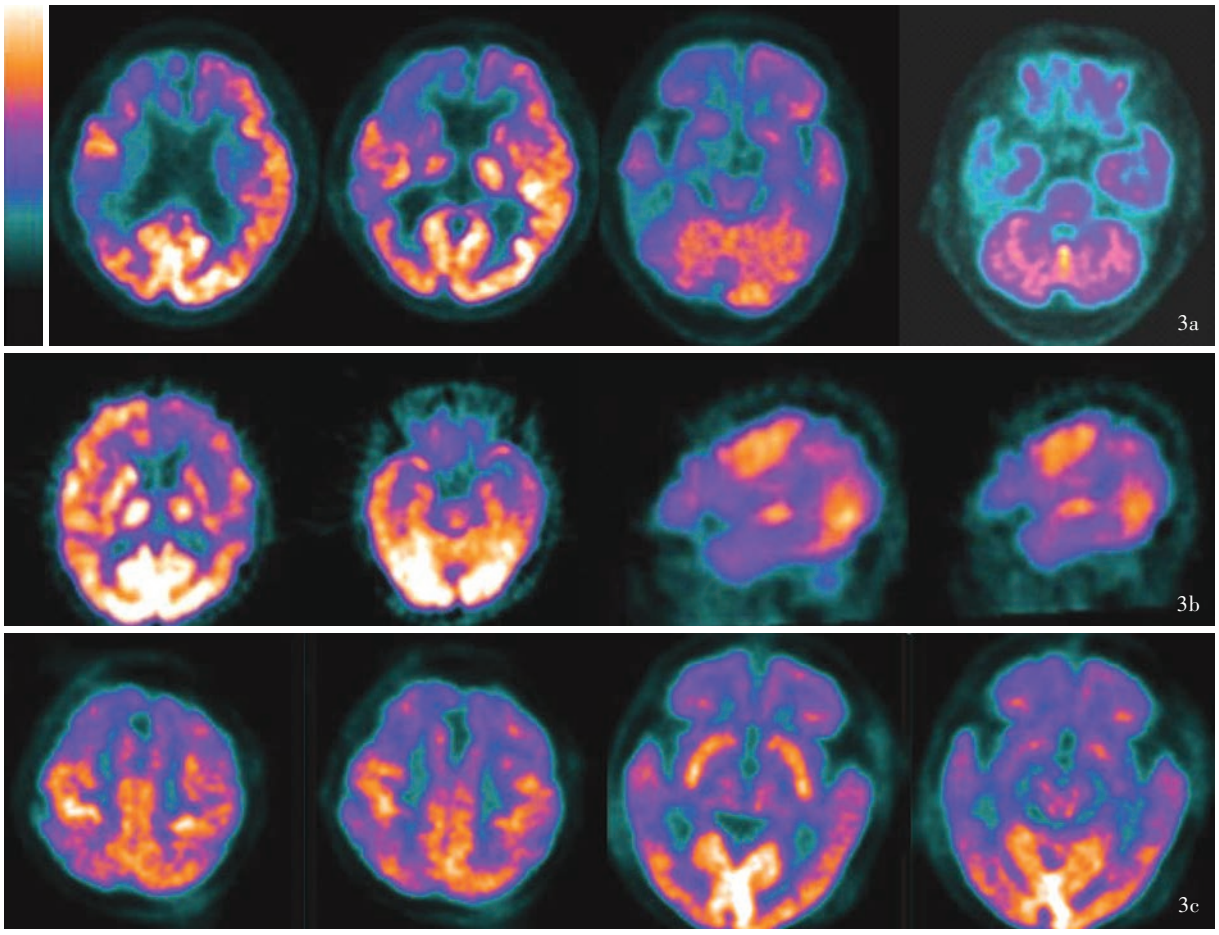


图3　额颞叶痴呆患者皮质代谢降低的3种模式　3a　女性患者，72岁。临床表现为明显行为异常，尤以脱抑制表现最为突出。连续横断面^{18}F-FDG PET显像，右侧额颞叶皮质代谢明显降低（蓝紫色区域所示），同时伴同侧基底节、丘脑代谢降低　3b　女性患者，57岁。表现为行为举止怪异且伴命名、找词困难等语言障碍。连续横断面^{18}F-FDG PET显像，左侧额颞叶皮质代谢明显降低（蓝紫色区域所示）；矢状位显像，左侧额叶和顶叶部分皮质代谢降低（蓝紫色区域所示），同侧基底节、丘脑代谢降低　3c　男性患者，62岁。主要表现为行为异常、执行能力减退、记忆力下降。连续横断面^{18}F-FDG PET显像，双侧额叶和前颞叶皮质呈基本对称性代谢降低（蓝紫色区域所示）

Figure 3　Three types of cortical hypometabolism in patients with FTD. A 72-year-old female patient presented with obvious abnormal behavior. Hypometabolic regions were presented in right frontotemporal lobe (blue purple areas) as well as in ipsilateral basal ganglia and thalamus on serial axial ^{18}F-FDG PET frames (Panel 3a). A 57-year-old female patient suffered from abnormal behavior and language impairment. The first 2 axial frames of ^{18}F-FDG PET showed obvious decreased activtity in left frontotemporal lobe (blue purple areas). Sagittal frames showed hypometabolism in partial cortex of left frontal and parietal lobe (blue purple areas) as well as in ipsilateral basal ganglia and thalamus (Panel 3b). A 62-year-old male patient with symptoms of abnormal behavior, decreased executive function and impairment of memory. Symmetric hypometabolism was found in bilateral frontal lobes and anterior temporal lobe in serial axial frames (blue purple areas, Panel 3c).

触缺失、特定脑区萎缩，早期表现为情景记忆缺失。额颞叶痴呆则为累及前额叶和前颞叶的一组病理异质性神经变性疾病，是仅次于阿尔茨海默病的临床常见神经变性疾病性痴呆[2]，以疾病早期出现人格和社会行为异常为主要症状，并贯穿病程始终。在实际医疗过程中，阿尔茨海默病与额颞叶痴呆临床表现之间存在明显交叉，额颞叶痴呆患者在病程早期也可存在记忆力减退等认知功能障碍，易被误诊为阿尔茨海默病，而许多阿尔茨海默病患者也因出现一些行为异常、情感精神症状而与额颞叶痴呆相混淆[11]。由于二者病理学机制不同，治疗方法亦不尽相同[3-4,12]，基于临床药物试验的纳入标准及具有针对性或特异性药物的临床应用，均对这两种痴呆类型的诊断与鉴别诊断提出了更高的要求，以免贻误诊断和治疗。例如，用于治疗阿尔茨海默病的胆碱酯酶抑制药对额颞叶痴呆无效，甚至有可能加重患者病情[3-4]。

葡萄糖是大脑的主要能量物质，^{18}F-FDG为葡萄

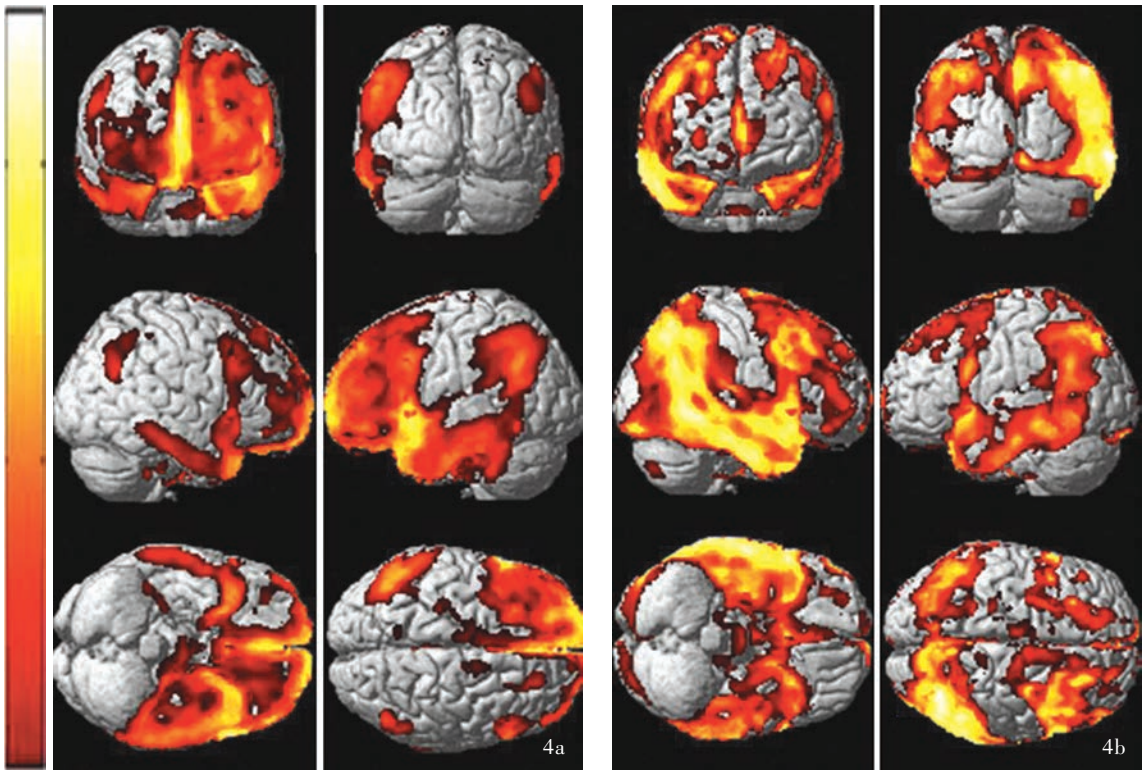


图4 各组受试者^{18}F-FDG PET显像的比较 4a 额颞叶痴呆组与对照组比较的SPM统计分析(显示阈值:$t=3.319$,$P=0.001$) 4b 阿尔茨海默病组与对照组比较的SPM统计分析(显示阈值:$t=3.319$,$P=0.001$)

Figure 4 SPM analysis of ^{18}F-FDG PET in AD and FTD groups compared with normal control group. Areas with significantly reduced glucose metabolism in FTD group compared with normal control group was projected on a three-dimensional standard. Figures obtained by SPM using a statistical threshold of $t=3.319$, $P=0.001$ (Panel 4a). Areas with significantly reduced glucose metabolism in AD group compared with normal control group was projected on a three-dimensional standard. Figures obtained by SPM using a statistical threshold of $t=3.319$, $P=0.001$ (Panel 4b).

糖类似物,以之为显像剂的PET显像方法,通过测定脑葡萄糖代谢率(CMRGlu)观察神经功能变化。前期研究表明,脑组织葡萄糖代谢与神经元活性相耦联,以^{18}F-FDG为显像剂的PET显像所显示的大脑皮质能量代谢变化,可以反映突触功能和密度,代表神经元功能状态[13-15]。国内关于这方面的研究刚刚开始,鲜见文献报道。

在本研究中,我们对阿尔茨海默病和额颞叶痴呆进行^{18}F-FDG PET显像,通过与正常对照组的对比,总结这两种痴呆类型的脑代谢降低特点。本研究所纳入病例虽无病理结果,但均严格依据临床诊断标准[10-11]获得明确诊断,并通过头部MRI检查排除其他中枢神经系统疾病和脑血管病。鉴于此,本研究入组病例均为较典型的阿尔茨海默病或额颞叶痴呆,行^{18}F-FDG PET显像时,阿尔茨海默病患者平均病程为4.80年、额颞叶痴呆为3.50年,两组患者皮质代谢降低程度均不属于疾病早期,虽然二者PET显像均表现为不同程度代谢降低,但阿尔茨海默病与额颞叶痴呆患者^{18}F-FDG PET所显示的脑代谢降低图型存在明显差异。

首先,皮质代谢降低部位不同。阿尔茨海默病低代谢脑区以大脑后部皮质为主,表现为明显的双侧顶颞叶皮质代谢降低,其程度和范围与症状严重性呈正相关(图1,2);由于处于病程较晚期,部分病例双侧额叶亦可见不同程度降低,但不如大脑后部颞顶叶皮质范围广泛、程度严重(图4),与相关文献报道基本一致[16-17]。额颞叶痴呆低代谢脑区主要集中在大脑前部,以额叶和前颞叶皮质为主,与文献报道相同[18-20],但也有与文献不同之处:本研究有部分病例顶叶亦同时受累,其顶叶背外侧皮质呈现低代谢,且不局限于与颞叶相邻的顶下区,可能与本研究所纳入病例病程较长有关。一项针对额颞叶痴呆患者开展的为期19.50个月的纵向随访研究显示,随着病情进展,额叶和前颞叶皮质代谢降低,并

逐渐累及顶叶[21]。近期也有文献报道,额颞叶痴呆患者颞顶叶皮质代谢降低也较常见[22]。

其次,双侧大脑半球皮质受累不对称程度不同。有18/20的患者双侧皮质受累程度和范围基本对称,仅2例表现为双侧不对称,但其中1例患者发病后32个月随访时低代谢脑区趋于对称(图2)。提示部分患者在病程进展过程中可存在双侧不平衡现象,但受累程度基本相同。大部分患者(16/20)额颞叶痴呆皮质低代谢脑区双侧不对称,以左侧更为显著。尽管有文献报道,部分病例表现为双侧受累大致相同[21],但大多数研究认为双侧大脑半球不对称现象更常见[18-20]。在Diehl-Schmid等[21]报告的一组额颞叶痴呆患者中,双侧大脑半球低代谢脑区不对称者约占90%。

第三,基底节和丘脑等皮质下结构受累程度不同。一般而言,病变同侧基底节、丘脑和(或)对侧小脑代谢降低在脑血管病和癫痫患者中更为常见,推测是由于皮质神经元损伤,引起神经投射路径和神经网络传导部位继发性功能异常所致。本研究部分额颞叶痴呆患者低代谢脑区同侧皮质下核团(基底节和丘脑)亦表现为代谢降低,而阿尔茨海默病患者则无明显变化。可能是由于额颞叶痴呆的病理学基础为叶性萎缩,其萎缩程度较阿尔茨海默病明显且累及额叶,与基底节、丘脑的神经投射密集、功能联系密切,因此严重的额叶代谢降低可继发基底节和丘脑代谢降低。而阿尔茨海默病呈弥漫性皮质轻度萎缩,且双侧大致对称,故其皮质下结构和功能改变不明显。

综上所述,阿尔茨海默病和额颞叶痴呆患者的脑代谢图型存在明显差异,可通过二者代谢降低累及的皮质部位、双侧是否对称、是否伴基底节和丘脑低代谢等特点进行鉴别。^{18}F-FDG PET显像可以增加临床诊断之准确性,对于临床诊断困难的患者是一种良好的辅助检查手段。

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·临床医学图像·

过渡型（混合性）脑膜瘤

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Transitional (mixed) meningioma

YAN Xiao-ling
Department of Pathology, Tianjin Huanhu Hospital, Tianjin 300060, China (Email: ll934065@126.com)

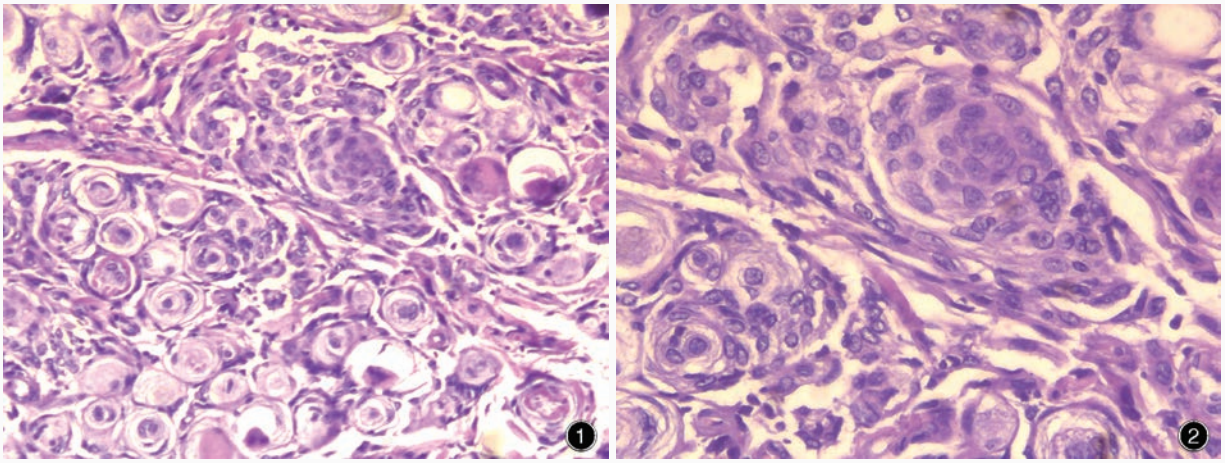

图1 光学显微镜观察肿瘤细胞排列成分叶状和束状结构，“漩涡”状结构明显 HE染色 低倍放大 **图2** 光学显微镜观察可见合体细胞岛结构 HE染色 中倍放大

Figure 1 Optic microscopy findings. Tumor cells were arranged as lobulated and fasciculated structure with obvious circinate form. HE staining low power magnified **Figure 2** Optic microscopy findings. Syncytial cell islands could be seen. HE staining medium power magnified

过渡型（混合性）脑膜瘤为脑膜瘤亚型之一，为临床常见类型。其组织学特征明显，具有脑膜皮细胞型和纤维型脑膜瘤，以及二者之间过渡的组织学特点（图1）；合体细胞岛结构与胶原丰富的梭形细胞混合排列（图2），“漩涡”状结构明显且丰富；同时可见较多砂粒体存在。

（天津市环湖医院病理科阎晓玲供稿）