·综述·

阿尔茨海默病早期诊断研究进展

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【摘要】 阿尔茨海默病是发病率较高且受到广泛重视的神经变性病，其发病机制尚未阐明，主要与β-淀粉样蛋白沉积、tau蛋白过度磷酸化、胆碱能神经元缺失有关。阿尔茨海默病的治疗以对症治疗为主，且无法逆转病程，因此早期诊断尤为重要。本文拟对近年阿尔茨海默病早期诊断研究进展进行综述，以期准确预测轻度认知损害进展至阿尔茨海默病进程，为早期诊断与有效治疗提供参考。

【关键词】 阿尔茨海默病； 综述

Research progress in early diagnosis of Alzheimer´s disease

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【Abstract】 Alzheimer´s disease (AD) is a kind of central nervous system degenerative disease with higher incidence, which has been paid increasing attention. The pathogenesis is not yet clear though it has been studied a lot. The existing theories focused on amyloid β-protein (Aβ) deposit, hyperphosphorylation of tau and cholinergic neuronal loss. There is mainly symptomatic treatment which cannot reverse disease course. So early diagnosis is particularly important for prevention and treatment of AD. The article will review recent advances in the studies of early diagnosis of AD. It may help accurately diagnose the process from mild cognitive impairment (MCI) to early AD and give advice on prevention and treatment.

【Key words】 Alzheimer disease; Review

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阿尔茨海默病(AD)是老年人群最常见的神经变性病，随着人口老龄化的加剧，其发病率逐年升高。根据《2009年世界阿尔茨海默病报告》数据，预计截至2030年全球阿尔茨海默病患者将达65.70×10^6例，截至2050年将达115.40×10^6例，尤其在中低收入国家的增长速度更快[1]。绝大多数患者未接受正规检查和诊断，因此未得到治疗，其中缺乏有效检测方法是最大障碍。迄今尚未发现一种足够准确的方法可以早期诊断并预测痴呆。

我国主要采用简易智能状态检查量表(MMSE)进行阿尔茨海默病早期筛查，但筛查出的患者多已进展至中至重度症状，较短时间内即出现认知功能明显减退[2]。美国最新的阿尔茨海默病诊断标准指出，阿尔茨海默病是包括轻度认知损害(MCI)在内的连续病程，并强调生物学标志物可以用于诊断阿尔茨海默病[3-4]。病程中出现神经退行性变和早期临床症状即可诊断为轻度认知损害[5]，由于阿尔茨海默病时期的50%病理改变在轻度认知损害时期即已发生，因此，生物学标志物可能诊断疾病并预测疾病进展[6]。

阿尔茨海默病包括病理生理学阶段和临床阶段，且病理改变开始时间较临床症状出现时间约早10年甚至更长[7]。一项针对早发型阿尔茨海默病的横断面研究显示，预期临床症状出现前25年脑脊液β-淀粉样蛋白42($A\beta_{42}$)水平即开始下降；预期临床症状出现前15年脑脊液tau蛋白水平升高，^{11}C-匹兹堡复合物B(^{11}C-PIB)PET可检测到脑组织Aβ沉积，脑萎缩加速；预期临床症状出现前10年出现脑组织葡萄糖低代谢和情景记忆障碍[8]。本文总结阿尔茨海默病早期检测与诊断方法，主要从阿尔茨海

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默病基因突变分析、影像学和生物学标志物测定如外周血和脑脊液检测等方面进行概述。

一、基因突变分析

近10年来，阿尔茨海默病遗传学和基因组学研究取得重大突破。研究显示，常染色体显性遗传性家族性阿尔茨海默病（FAD）仅占全部阿尔茨海默病的小部分，而占绝大部分的散发性阿尔茨海默病是多种易感基因共同作用的结果[9-10]。无痴呆人群也可以检测到易感基因位点，易感基因可能在疾病早期即已发挥作用，且疾病晚期在认知损害方面具有更高的易感性。尽管对于携带者而言，单一易感基因的作用较小，但全基因组中多种易感等位基因累加则使个体处于高危状态[11]。评价总遗传风险与阿尔茨海默病前期临床和影像学表现相关性的研究显示，多基因风险评分有助于鉴别诊断和预测阿尔茨海默病患病风险人群[9]。除4种已确定的阿尔茨海默病相关基因外，近年采用全基因组相关性研究（GWAS）发现新的基因位点，可能成为疾病诊断的生物学标志物。

1. *APP*、*PS-1*、*PS-2*、*ApoE* 等Aβ代谢相关基因　既往研究显示，β-淀粉样前体蛋白（*APP*）、早老素1（*PS-1*）、早老素2（*PS-2*）基因突变可以导致早发性阿尔茨海默病（EOAD），而载脂蛋白E（*ApoE*）基因与晚发性阿尔茨海默病（LOAD）相关[10]。*APP*、*PS-1*、*PS-2* 基因突变导致Aβ生成并沉积，*ApoE* 基因参与脂质运输，影响Aβ清除，其中，*ApoEε4* 等位基因与阿尔茨海默病密切相关，其频率在晚发性阿尔茨海默病患者中明显升高[12]。簇集素（*CLU*）基因与 *ApoE* 基因相似，参与Aβ构型转变，抑制其沉积。α2巨球蛋白（*A2M*）基因通过结合Aβ以减少其沉积，其突变时减慢Aβ清除速度。既往研究显示，*A2M* 基因外显子2缺失可以使阿尔茨海默病患病风险增加数倍[13]。因此，进行上述基因检测可以早期预测阿尔茨海默病。

2. *Tau*、*PIN1* 等tau蛋白相关基因　Tau蛋白是微管相关蛋白（MAP），其翻译后修饰异常与阿尔茨海默病发病有关，过磷酸化表达可以降低其与微管的亲和力，导致神经原纤维缠结（NFTs）形成。尽管尚未确定 *tau* 基因突变与早发性阿尔茨海默病的关系，但是确定其可以导致一系列晚发性阿尔茨海默病[14]。绝大多数 *tau* 基因错义突变可以降低tau蛋白与微管的亲和力，尤其是外显子10突变，其次是外显子9和12突变，而外显子13突变的影响较小；尚有一些错义突变可以直接刺激tau蛋白形成纤维丝[15]。因此对上述基因突变进行早期检测和干预，可以减少神经细胞和神经胶质细胞变性以及阿尔茨海默病的发病。此外，肽基脯氨酰基顺反异构酶（PPIase）可以特异性调节某些磷酸化蛋白构象变化，而阿尔茨海默病患者发生PPIase蛋白氧化抑制，从而无法调节过磷酸化的tau蛋白构象，使其恢复生物学功能[16]。研究显示，*PIN1* 基因多态性加速神经退行性变和临床病程，其中-842C>G单核苷酸多态性（SNP）参与轻度认知损害到阿尔茨海默病的转变[16]，对早期诊断阿尔茨海默病具有一定意义。

3. *CR1*、*CD33* 等免疫应激反应相关基因　当细胞外积聚Aβ时，小胶质细胞进行吞噬，同时触发炎症反应过程，启动自身免疫应激反应。补体系统长期激活和炎症反应与阿尔茨海默病的神经病理学过程有关，全基因组相关性研究显示，补体受体1（*CR1*）基因多态性与晚发性阿尔茨海默病相关；阿尔茨海默病患者发生小胶质细胞TYRO蛋白酪氨酸激酶结合蛋白（*TYROBP*）和髓样细胞触发性受体2（*TREM2*）基因突变，突变的 *TREM2* 基因和表达上调的 *CD33* 基因可以抑制Aβ清除，从而增加阿尔茨海默病患病风险[17-18]。

4. 其他阿尔茨海默病相关基因多态性　研究显示，亦有一些基因多态性与阿尔茨海默病的患病风险相关，例如，位于第12号染色体的低密度脂蛋白受体相关蛋白1（*LRP1*）基因是阿尔茨海默病的危险因素，可以调节ApoE相关轴突生长和APP相关神经元代谢，增加Aβ生成和延缓Aβ清除；肿瘤坏死因子-α（*TNF-α*）和前列腺素内过氧化物合成酶2（*PTGS2*）基因通过炎症反应以增加阿尔茨海默病患病风险[19-20]。Meta分析显示，白细胞介素（*IL*）基因多态性与阿尔茨海默病患病风险相关[21]。

晚近出现很多关于阿尔茨海默病患病风险基因位点的研究报道，详见表1，这些基因检测对早期诊断和预测阿尔茨海默病发生与发展有一定作用。

二、影像学检查

影像学技术的发展对阿尔茨海默病的诊断与预后判断具有重要意义。目前临床最常用的影像学方法主要是MRI和PET。

1. MRI检查　MRI是在外加磁场作用下激发人体内氢原子核吸收能量而产生跃迁，射频（RF）脉冲停止后由于不同内部结构产生不同衰减而发射特定频率信号，经仪器接收后处理绘制出内部结构图

表1 阿尔茨海默病相关易感基因

Table 1. Susceptibility genes associated with AD

Susceptibility gene	Gene mapping	Type of AD	Mechanism
APP[22-23]	21q21	EOAD/LOAD	Aβ production
PS-1[22-23]	14q24.3	EOAD/LOAD	Aβ production
PS-2[22-23]	1q31-q42	EOAD/LOAD	Aβ production
ApoE[22-24]	19q13.2	LOAD	Aβ clearance
CLU[25-26]	8p21-p12	LOAD	Cholesterol metabolism, Aβ clearance
ABCA7[27]	19p13.3	LOAD	Cholesterol metabolism, Aβ clearance
SORL1[28-29]	11q23.2-q24.2	LOAD	Cholesterol metabolism, Aβ production
CR1[25]	1q32	LOAD	Aβ clearance, inflammatory reaction
CD33[18]	19q13.3	LOAD	Aβ clearance, inflammatory reaction
MS4A[18]	11q12.1	LOAD	Inflammatory reaction
EPHA1[18]	7q34	LOAD	Endocytosis
TREM2[17]	6p21.1	LOAD	Inflammatory reaction
BIN1[28]	2q14	LOAD	Aβ production, endocytosis
PICALM[25]	11q14	LOAD	Aβ production, Aβ clearance
CD2AP[18]	6q12	LOAD	Endocytosis
PLD3[28]	19q13.2	LOAD	Endocytosis
HLA-DRB5/DRB1[17,29]	6p21.3	LOAD	Inflammatory reaction
INPP5D[17]	2q37.1	LOAD	Inflammatory reaction
MEF2C[29]	5q14.3	LOAD	Inflammatory reaction, synaptic function
PTK2B[29]	8p21.1	LOAD	Cell migration, synaptic function
NME8[28]	7p14.1	LOAD	Cytoskeleton function, axonal transportation
CASS4[28]	20q13.31	LOAD	APP and tau metabolism
FERMT2[29]	14q22.1	LOAD	Tau metabolism

APP，amyloid β-protein precursor，β-淀粉样前体蛋白；PS-1，presenilin-1，早老素1；PS-2，presenilin-2，早老素2；ApoE，apolipoprotein E，载脂蛋白E；CLU，clusterin，簇集素；CR1，complement receptor 1，补体受体1；TREM2，triggering receptor expressed on myeloid cells 2，髓样细胞触发性受体2；EOAD，early-onset Alzheimer's disease，早发性阿尔茨海默病；LOAD，late-onset Alzheimer's disease，晚发性阿尔茨海默病；Aβ，amyloid β-protein，β-淀粉样蛋白

像的影像学技术。MRI对软组织具有较好的分辨力，可以检测出阿尔茨海默病患者脑萎缩如脑室扩大、脑沟增宽等。研究显示，轻度认知损害进展至阿尔茨海默病的过程中出现胼胝体萎缩，且女性轻度认知损害进展期胼胝体萎缩速度快于轻度认知损害非进展期，因此，胼胝体萎缩可能成为预测轻度认知损害进展至阿尔茨海默病的标记，尤其是女性患者[30]。神经病理学和结构性MRI（sMRI）研究显示，内侧颞叶是阿尔茨海默病最早受累脑区，且轻度认知损害期即检出海马和内嗅皮质（EC）体积缩小，海马旁回体积稍缩小；此外，外侧颞叶萎缩也可能预测轻度认知损害进展至阿尔茨海默病[31]。胼胝体、杏仁体、海马等不同部位变化和变化速度可以用来鉴别阿尔茨海默病与其他神经变性病及其病程阶段。扩散张量成像（DTI）是在MRI基础上施加多方向扩散敏感梯度而获得图像的技术，对脑白质微结构改变十分敏感。研究显示，DTI可以鉴别诊断阿尔茨海默病患者、轻度认知损害患者与正常人群[32]；阿尔茨海默病和轻度认知损害患者胼胝体和扣带回部分各向异性（FA）值差异有统计学意义，可以作为早期诊断阿尔茨海默病和评价病程进展的指标[33]。fMRI可以检测神经功能连接改变，研究显示，额叶、顶叶、扣带回和内侧颞叶功能连接改变可以早期识别轻度认知损害[34]。

2. PET显像 PET显像是利用同位素示踪原理，显示示踪剂分布和变化的一项功能成像技术。近年来，PET显像预测轻度认知损害进展至阿尔茨海默病业已成为研究热点，主要有^{18}F-脱氧葡萄糖（^{18}F-FDG）PET和Aβ-PET。（1）^{18}F-FDG PET：阿尔茨海默病患者脑组织葡萄糖代谢变化的最早证据来自1983年de Leon等[35]的研究，他们采用^{18}F-FDG PET检测脑组织葡萄糖代谢率，并认为葡萄糖代谢率与认知功能相关。后续研究显示，阿尔茨海默病轻中度阶段颞顶叶、后扣带回和楔前叶葡萄糖代谢降低；进展期额叶葡萄糖代谢降低；阿尔茨海默病患者脑组织葡萄糖代谢降低区域主要集中于脑桥、感觉运动皮质（SMC）、初级视觉皮质、基底节、丘脑和小脑，与其他类型痴呆有所不同[36]。因此提出，^{18}F-FDG PET显示的内侧颞叶葡萄糖低代谢是诊断轻度认知损害敏感性和特异性较高的方法[31]。但是由于既往^{18}F-FDG PET研究缺乏标准化诊断程序，目前证据不支持其作为轻度认知损害患者的常规临床检测项目[37]，因此，将^{18}F-FDG PET诊断程序标准化是前提。（2）Aβ-PET：是一项与Aβ结合的示踪剂成像技术。一项关于正常老年人群的生物学标志物研究显示，Aβ沉积与脑结构和神经功能改变有关，且与轻度认知损害或阿尔茨海默病的病理改变相一致[7]。一项^{11}C-PIB PET研究显示，存在Aβ沉积的51例轻度认知损害患者中29例（56.86%）进展至阿尔茨海默病，而无Aβ沉积的17例轻度认知损害患者中1例（5.88%）进展至阿尔茨海默病；75～89岁存在Aβ沉积的轻度认知损害患者若已出现情

景记忆障碍，其从轻度认知损害进展至阿尔茨海默病的概率上升至80%[38]。脑组织Aβ沉积是阿尔茨海默病发病的标记，其在无症状阶段即已对认知功能产生影响，先于脑组织葡萄糖代谢改变；至疾病中后期，葡萄糖代谢降低更加显著，与进行性认知功能障碍密切相关[39]。因此，Aβ-PET适用于阿尔茨海默病的早期诊断，而^{18}F-FDG PET适用于病程进展的监测。一项研究比较^{18}F-FDG PET、^{11}C-PIB PET与MRI在轻度认知损害进展至阿尔茨海默病的预测价值，结果显示，MRI的预测准确度最高，为67%；且三者任意组合中MRI联合^{11}C-PIB PET的预测准确性最高，为76%；而^{11}C-PIB PET的敏感性最高，^{18}F-FDG PET最低[40]。总之，通过各种PET显像技术的联合以实现阿尔茨海默病的早期诊断是可行的。目前，大多数PET显像研究均针对Aβ沉积特征，示踪剂还包括^{18}F-Florbetaben、^{18}F-Flutemetamol和^{18}F-Florbetapir[41]。期待越来越多针对神经退行性变、神经炎症反应和神经递质传递障碍的影像学研究出现。

三、生物学标志物

阿尔茨海默病的病理改变并不局限于脑组织，其他组织中也可以观察到相关分子病理改变。生物学标志物可以提高早期诊断的准确性，主要包括外周血、脑脊液和尿液生物学标志物（表2）。

表2 外周血和脑脊液生物学标志物

Table 2. Peripheral blood and CSF biomarkers

Biomarker	Peripheral blood	CSF
Aβ and tau[42-44]	T-tau, platelet APP isomer, platelet tau content	T-tau, p-tau, $A\beta_{42}$
Correlation factor of immunization and inflammation, oxidative stress[45-46]	IL-6, IL-1β, IL-12, IL-18, TGF-β, TNF-α	TGF-β, CHI3L1/YKL-40, SOD, MDA
miRNA[47-51]	miRNA-9-5p, miRNA-106a-5p, miRNA-106b-5p, miRNA-107, miRNA-590-5p, miRNA-142-5p, miRNA-194-5p, miRNA-9, miRNA-125b, miRNA-146a, miRNA-181c, let-7g-5p, miRNA-191-5p	miRNA-9, miRNA-128, miRNA-146a, let-7i-5p, miRNA-15a-5p, miRNA-29c-3p, miRNA-29a, miRNA-29b, miRNA-34a, miRNA-125b, miRNA-199b-5p, miRNA-22-5p, miRNA-206

CSF，cerebrospinal fluid，脑脊液；Aβ，amyloid β-protein，β-淀粉样蛋白；t-tau，total tau，总tau蛋白；APP，amyloid β-protein precursor，β-淀粉样前体蛋白；p-tau，phosphorylated tau，磷酸化tau蛋白；IL，interleukin，白细胞介素；TGF-β，transforming growth factor-β，转化生长因子-β；TNF-α，tumor necrosis factor-α，肿瘤坏死因子-α；CHI3L1/YKL-40，chitinase-3-like protein 1，几丁质酶-3样蛋白-1；SOD，superoxide dismutase，超氧化物歧化酶；MDA，malondialdehyde，丙二醛；miRNA，microRNA，微小RNA

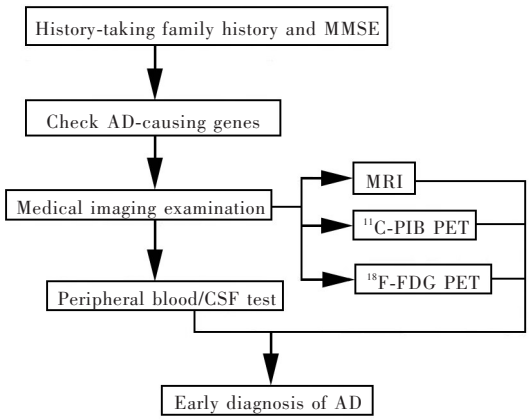
1. Aβ和tau蛋白测定　目前的脑脊液生物学标志物有较高的准确性，如脑脊液总tau蛋白（t-tau）、磷酸化tau蛋白（p-tau）升高和$A\beta_{42}$降低是早期鉴别诊断阿尔茨海默病与其他痴呆的有效生物学标志物[42]。研究显示，阿尔茨海默病患者脑脊液检查较Aβ-PET更早检出Aβ沉积[52]。Palmqvist等[53]发现，脑脊液Aβ水平异常患者脑组织Aβ沉积速度与脑脊液和Aβ-PET均异常患者相近，是脑脊液和Aβ-PET均正常患者的3倍以上，且脑脊液和Aβ-PET均异常患者在海马结构方面的恶化更严重，提示其更接近阿尔茨海默病，故脑脊液生物学标志物可以更好地早期诊断阿尔茨海默病。多项研究比较轻度认知损害进展期与稳定期患者脑脊液tau蛋白和$A\beta_{42}$表达变化，其结果显示，轻度认知损害进展期患者脑脊液tau蛋白显著升高，$A\beta_{42}$显著下降[54-55]。Olsson等[43]认为，脑脊液t-tau蛋白、p-tau蛋白和$A\beta_{42}$可以较好地区分阿尔茨海默病患者与正常对照者以及轻度认知损害进展期与稳定期，血浆t-tau蛋白可以较好地区分阿尔茨海默病患者与正常对照者。阿尔茨海默病患者血小板中不同类型tau蛋白比例与正常对照者不同[56]，故血小板tau蛋白水平也可能成为阿尔茨海默病早期诊断的生物学标志物。血小板APP异构体蛋白表达变化与阿尔茨海默病相关，阿尔茨海默病患者高相对分子质量APP异构体/低相对分子质量APP异构体比值下降，且下降程度与疾病严重程度相关，有较好敏感性和特异性[44]。

2. 免疫炎症和氧化应激相关因子测定　免疫炎症相关因子在阿尔茨海默病发生与发展中发挥重要作用，包括白细胞介素家族、转化生长因子（TGF）家族和肿瘤坏死因子（TNF）家族等。有研究显示，阿尔茨海默病患者脑脊液TGF-β水平升高，而IL-6、IL-1β和TNF-α无明显变化[45]；阿尔茨海默病患者外周血IL-6、IL-1β、IL-12、IL-18、TGF-β和TNF-α水平升高，而IL-4、IL-8、IL-10、干扰素-γ（INF-γ）和C-反应蛋白（CRP）无明显变化。近年有研究显示，脑脊液免疫炎症相关神经颗粒素和几丁质酶-3样蛋白-1（CHI3L1/YKL-40）水平升高可以反映阿尔茨海默病病程[46]。氧化应激相关因子有助于早期诊断阿尔茨海默病，氧化、过氧化和超氧化过程可以导致蛋白质、脂质、DNA等改变，其活动度和产物水平在阿尔茨海默病患者、轻度认知损害患者和正常对照者中存有差异，如轻度认知损害患者和阿尔茨海默病

患者超氧化物歧化酶(SOD)活性较正常对照者降低,丙二醛(MDA)水平较正常对照者升高[57]。

3. 微小RNA测定 近年越来越多研究显示,微小RNA(miRNA)可以影响*APP*、*PS-1*、*PS-2*和淀粉样前体蛋白β位点剪切酶-1β(*BACE-1*)基因在脑组织中的表达变化,对神经生长分化起重要作用[58]。阿尔茨海默病患者海马组织miRNA-9、miRNA-128、miRNA-146a表达上调,尤以miRNA-146a与脑组织炎症反应的关系最密切[47-48]。脑脊液可检出52种miRNA,与正常对照者相比较,阿尔茨海默病患者miRNA-15a-5p和let-7i-5p表达上调,miRNA-29c-3p表达下调[49],表明脑脊液miRNA表达变化可以鉴别诊断阿尔茨海默病。Kiko等[59]研究显示,与正常对照者相比,阿尔茨海默病患者脑脊液miRNA-29a和miRNA-29b表达上调,miRNA-34a、miRNA-125b和miRNA-146a表达下调。此外,阿尔茨海默病患者脑脊液miRNA-199b-5p、miRNA-22-5p和miRNA-206表达亦上调[49]。外周血miRNA表达变化也可以为阿尔茨海默病的临床预测提供参考。晚近研究显示,与阿尔茨海默病易感性相关的7种miRNA中,miRNA-9-5p、miRNA-106a-5p、miRNA-106b-5p和miRNA-107表达下调可以增加阿尔茨海默病患病风险,其中miRNA-106a-5p作为预测因素,其灵敏度68%,特异度93%;miRNA-29a-3p、miRNA-125a-3p和miRNA-125b-5p则无明显变化[50]。外周血可以检出168种miRNA,与正常对照者相比,阿尔茨海默病患者miRNA-590-5p和miRNA-142-5p表达上调,miRNA-194-5p表达下调[49]。目前研究最多的6种miRNA为miRNA-9、miRNA-125b、miRNA-146a、miRNA-181c、let-7g-5p和miRNA-191-5p,最有希望成为早期诊断阿尔茨海默病的生物学标志物[51]。尽管目前对miRNA的研究尚不充分,仍待更大规模临床研究的验证,但是未来有望可以通过几种miRNA组合以诊断不同类型痴呆。

4. 检测技术 除生物学标志物外,检测技术也应受到重视。小分子或蛋白质检测通常采用质谱法(MS),免疫分析如酶联免疫吸附试验(ELISA)或两种方法形成酶联免疫质谱测定技术。近年出现多种超灵敏检测平台,如单分子计数(SMC)、单分子阵列(Simoa)、免疫磁减量(IMR)等,不仅适用于血液检测,也适用于脑脊液低水平生物学标志物检测。如采用Simoa法测定血清Aβ和t-tau蛋白以预测神经功能,采用IMR法测定血浆t-tau蛋白以区分阿尔茨海默病患者与正常对照者[60]。采用SMC法可以检出阿尔茨海默病患者脑脊液高水平视锥蛋白样蛋白1,也可以检出脑脊液低水平Aβ低聚物以区分阿尔茨海默病患者、轻度认知损害患者与正常对照者[61]。上述检测技术尚未普及,但前景可观。



MMSE, Mini-Mental State Examination, 简易智能状态检查量表; AD, Alzheimer's disease, 阿尔茨海默病; ^{11}C-PIB, ^{11}C-Pittsburgh complex B, ^{11}C-匹兹堡复合物B; ^{18}F-FDG, ^{18}F-fluoro-2-deoxy-D-glucose, ^{18}F-脱氧葡萄糖; CSF, cerebrospinal fluid, 脑脊液

图1 阿尔茨海默病早期诊断流程图

Figure 1 Flow diagram of AD's early diagnosis.

四、问题与展望

上述检测方法可以辅助判断阿尔茨海默病病理学过程,有助于其早期诊断,但存在以下不足:首先,由于基因的复杂性和样本量的局限性,晚发性阿尔茨海默病相关基因位点有待验证。其次,影像学检查不如生物学标志物敏感性高,而脑脊液采集存在一定风险,外周血检测尚不成熟。而且,生物学标志物的特异性方面存在局限性,如^{18}F-FDG PET显像,葡萄糖代谢是非特异性指标,多种原因如缺血、炎症反应等均可以影响葡萄糖代谢,可能与阿尔茨海默病病程无直接关系[62]。此外,生物学标志物虽然可以在无症状阶段进行预测,但单一指标一般不足以确定为一种疾病,结果可能与预测方向存在差异[7]。因此,多方面、多指标相结合进行诊断至关重要。人为因素也不可忽视,不同研究团队对一些潜在生物学标志物的研究可能由于地域局限性和技术方法的不同而存在争议,尚待扩大样本量并统一研究方法以期获得一致性结论。

本文总结较为综合的阿尔茨海默病早期诊断方法,参见图1。对临床前阿尔茨海默病或轻度认

知损害患者进行早期诊断，首先应询问患者或知情人相关病史，基于提供的信息和MMSE量表进行认知功能评价。如果患者有阿尔茨海默病家族史或年龄<65岁即有认知损害倾向，从其外周血中提取基因组DNA以检测是否携带致病性基因，包括*APP*、*PS-1*和*PS-2*。若无明显临床症状，则应进行影像学检查，首选^{11}C-PIB PET，且与MRI相结合准确性较高。如果需要更加精细地诊断与预测，可以采集脑脊液进行检查。外周血检测尚待更多研究和验证，虽然前景广阔，但目前笔者仍推荐通过MRI、^{11}C-PIB PET和脑脊液检查相结合的方法进行阿尔茨海默病早期诊断。

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·临床医学图像·

Wallerian变性

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Wallerian degeneration

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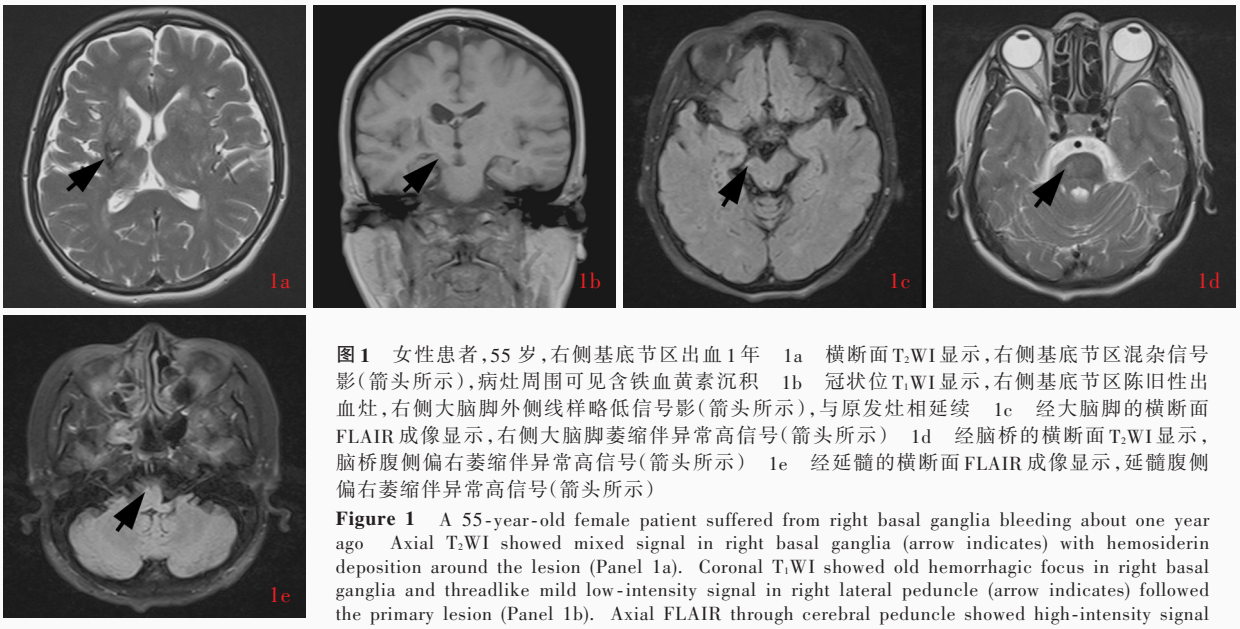

图1 女性患者,55岁,右侧基底节区出血1年 1a 横断面T_2WI显示,右侧基底节区混杂信号影(箭头所示),病灶周围可见含铁血黄素沉积 1b 冠状位T_1WI显示,右侧基底节区陈旧性出血灶,右侧大脑脚外侧线样略低信号影(箭头所示),与原发灶相延续 1c 经大脑脚的横断面FLAIR成像显示,右侧大脑脚萎缩伴异常高信号(箭头所示) 1d 经脑桥的横断面T_2WI显示,脑桥腹侧偏右萎缩伴异常高信号(箭头所示) 1e 经延髓的横断面FLAIR成像显示,延髓腹侧偏右萎缩伴异常高信号(箭头所示)

Figure 1 A 55-year-old female patient suffered from right basal ganglia bleeding about one year ago Axial T_2WI showed mixed signal in right basal ganglia (arrow indicates) with hemosiderin deposition around the lesion (Panel 1a). Coronal T_1WI showed old hemorrhagic focus in right basal ganglia and threadlike mild low-intensity signal in right lateral peduncle (arrow indicates) followed the primary lesion (Panel 1b). Axial FLAIR through cerebral peduncle showed high-intensity signal and atrophy of right cerebral peduncle (arrow indicates, Panel 1c). Axial T_2WI through the pons showed high-intensity signal and atrophy in the ventral pons (arrow indicates, Panel 1d). Axial FLAIR through the medulla showed high-intensity signal and atrophy in ventral medulla (arrow indicates, Panel 1e).

Waller于1850年率先描述动物周围神经离断后,远端轴索及其髓鞘顺行性改变,称为Wallerian变性(WD)。中枢神经系统Wallerian变性系神经元胞体损害或轴突离断后,远端和部分近端轴索及其髓鞘变性、崩解过程。任何导致皮质和皮质下神经纤维通路功能障碍的病变,如缺血性或出血性卒中、肿瘤、脱髓鞘病变、颅脑创伤、手术等均可以导致Wallerian变性。皮质脊髓束最易受累,额桥束、枕颞顶桥束、胼胝体、脑桥-小脑通路、乳头体-丘脑通路、海马-穹窿-乳头体通路亦可受累。影像学改变与病理学特征相关:原发灶损伤后3~4周,相应通路轴索变性,MRI平扫无明显异常,扩散张量成像(DTI)可以早期发现急性期轴索及其髓鞘异常导致的部分各向异性(FA)值降低;至5~10周,相应通路髓鞘蛋白崩解,轴索和髓鞘肿胀,由于髓鞘脂质尚完整(脂质含量相对增加),T_2WI呈低信号;至10~14周,髓鞘脂质崩解,含水量增加,神经胶质细胞增生,T_1WI呈等或稍低信号、T_2WI和FLAIR成像呈高信号;数月后受累通路呈线样长T_1、长T_2信号改变,变性纤维束所在脑区萎缩。FLAIR成像和T_2WI对上述病理改变最敏感,是首选影像学检查方法,而CT仅能显示相应结构萎缩。皮质脊髓束Wallerian变性特征性表现为与原发灶相连(图1a)且与纤维束走行相一致的连续和(或)不连续条形T_1WI低信号(图1b)、FLAIR成像或T_2WI高信号(图1c~1e),横断面可见患侧大脑脚(图1c)、脑桥腹侧(图1d)、延髓腹侧锥体(图1e)萎缩。发生于锥体束、额桥束、枕颞顶桥束的Wallerian变性应与脑干亚急性缺血性卒中、脱髓鞘病变相鉴别;以双侧桥臂异常信号为特征的脑桥-小脑通路Wallerian变性应与桥臂缺血性卒中、感染和脱髓鞘病变相鉴别。

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