·标准与规范·

中国痴呆与认知障碍诊治指南(四):辅助检查及其选择

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在痴呆的诊断流程中,辅助检查是必需的,能为我们确定痴呆和认知障碍的类型提供有力的证据。辅助检查包括体液检查、影像学检查、电生理检查、基因检查,各项检查在不同痴呆和认知障碍类型诊断中价值也不相同,正确理解和判读显得十分重要。

写作组参考了国内外近期发表的相关临床研究、荟萃分析和系统性综述,以循证医学结果为依据,并结合我国实际情况,编写了辅助检查及其选择,希望能指导临床医师选择恰当的实验室检查。文献证据级别和推荐强度标准参见本杂志刊载系列中的《中国痴呆与认知障碍指南(一):痴呆诊断流程》一文(见本刊2011年91卷第9期577-581页)。

一、体液检测

1. 血液和尿液检查:血液的实验室检查是痴呆与认知障碍患者总体筛查的重要组成部分。血液的检测目的包括:(1)发现存在的伴随疾病或并发症;(2)发现潜在的危险因素;(3)揭示痴呆的病因。例如在阿尔茨海默病(AD)中,血常规(全血细胞计数和分类计数)、血电解质、生化检查、甲状腺功能检查(TSH)、维生素B12水平、梅毒的血清学检查等和尿常规均正常,这些检查可以排除能导致和诱发认知障碍的代谢性疾病,例如甲状腺功能低下、肝性脑病、恶性贫血、尿毒症、低钠血症和目前已少见的Ⅲ期梅毒等。血清学生化标志物一直是痴呆与认知障碍的研究热点。如AD的常见血清学生化标志物包括淀粉样蛋白(Aβ蛋白、Aβ自身抗体、血小板淀粉样前体蛋白亚型)等[1-2]。但迄今为止,尚没有一项血清学生化标志物能够用于AD的临床诊断。其他的痴呆与认知障碍疾病同样缺乏特异、敏感的血清学生化标志物。也无尿液生化标志物检查用于痴呆与认知障碍的临床诊断。

【推荐】

对所有首次就诊的患者进行以下血液学检测有助于揭示认知障碍的病因或发现伴随疾病:全血细胞计数、红细胞沉降率、血电解质、血钙、血糖、肝肾功能和甲状腺素(TSH)水平,在有些患者常需要进行更多的检测如:维生素B12、梅毒血清学检测、HIV、伯氏疏螺旋体等【专家共识】。

血液和尿液生化标志物检查不作为痴呆与认知障碍的临床诊断的常规检查【专家共识】。

2. 脑脊液检查:脑脊液(CSF)除了常规检查外,可检查一些特殊蛋白如:β淀粉样蛋白(Aβ)、总tau蛋白(T-tau)、磷酸化tau蛋白(P-tau)、14-3-3蛋白含量的检测,有助于了解痴呆病因,区别痴呆与非痴呆人群[3](Ⅱ级证据),并一定程度上有助于鉴别不同痴呆亚型[4](Ⅲ级证据)。(1)Aβ42检测:AD患者脑脊液β淀粉样蛋白Aβ42水平降低。一项Meta分析显示,脑脊液中Aβ42含量有利于鉴别AD与正常人,其敏感性和特异性分别为86%和90%[5](Ⅲ级证据)。额颞叶变性(FTD)[6-7]、路易体痴呆(DLB)[8]、血管性痴呆(VaD)[9-10]和Creutgfeldt-Jakob disease(CJD)[11]患者的脑脊液中Aβ42水平也有不同程度降低。有报道比较脑脊液中Aβ42蛋白含量的差异,鉴别AD与额颞叶痴呆、血管性痴呆,其特异性分别为59%~81%[6-7,12]和71%[6](Ⅱ级证据)。还有研究显示检测Aβ40/Aβ42比值可提高AD诊断的敏感性和特异性[13](Ⅲ级证据)。(2)T-tau检测:AD、VaD、CJD、FTD痴呆患者T-tau水平均有不同程度升高,但DLB患者脑脊液T-tau含量通常为正常范围[8](Ⅱ级证据)。CJD患者脑脊液中T-tau含量常高于AD,敏感性和特异性分别为93%和90%~100%[14-17](Ⅰ级证据),T-tau极度

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升高多提示CJD可能。T-tau在AD组患者脑脊液中含量较与其年龄相匹配的非痴呆的其他神经系统疾病组高，其特异性可达90%[5]（Ⅱ级证据），但其对AD敏感度相对较低为64%[18]～81%[5]（均Ⅲ级证据）。目前脑脊液T-tau检测有利于鉴别AD与非痴呆患者，但不能有效区分痴呆亚型。（3）P-tau检测：检测脑脊液中P-tau蛋白含量，有助于从MCI患者中筛查出AD[19]（Ⅲ级证据）。P-tau/T-tau比值有助于鉴别不同类型痴呆，AD患者中P-tau/T-tau比值较CJD组患者高，有助于两者鉴别[20]（Ⅰ级证据）。Tau蛋白磷酸化位点不同在诊断中的意义受到关注，目前已发现Tau蛋白P-tau 181、P-tau 231、P-tau 199三种不同磷酸化位点对不同痴呆类型鉴别作用不同。①P-tau 231：对AD与FTD，以及AD与非痴呆患者（与AD组相匹配其他神经系统疾病对照组）的鉴别力高[21]（Ⅱ级证据）；区分AD与抑郁导致假性痴呆的鉴别中，对AD特异性可达87%[22]（Ⅰ级证据），可鉴别AD与FTD（敏感性和特异性分别为88.0%～90.2%和80.0%～92.0%）[22-23]（Ⅰ级证据）；P-tau231含量变化可预测MCI向AD转化（敏感性和特异性分别为66.7%～100.0%和66.7%～77.8%）[24]（Ⅰ级证据）。②P-tau199：对AD与非AD鉴别的敏感性和特异性较P-tau231略弱，分别为85.2%和85.0%[22]（Ⅰ级证据）。③P-tau181：AD与DLB鉴别中对AD的敏感性和特异性分别为94%和64%[23]（Ⅰ级证据），与FTD鉴别，对AD的敏感性和特异性分别为68.4%和85.7%[25]（Ⅰ级证据），与特发性正常颅压脑积水鉴别分别为88.7%和86.7%[26]（Ⅰ级证据）。同时检测P-tau 181、P-tau 231、P-tau 199三种不同磷酸化位点tau蛋白含量，能提高对AD患者诊断准确率。P-tau181/T-tau比值可提高对AD与正常老化鉴别，对AD敏感性和特异性分别为92.5%和100.0%（Ⅰ级证据）。P-tau231与P-tau 199联合检测也可提高从神经系统疾病中诊断AD正确率，对AD鉴别敏感性及特异性可达80%～90%之间[18]（Ⅲ级证据）。（4）Aβ42和Tau联合检测：对病理确诊病例的研究显示，Aβ42和Tau联合检测可提高AD与非痴呆、FTD鉴别的敏感性和特异性[27-29]（Ⅰ级证据）。联合检测Aβ42和P-tau是目前AD与非AD痴呆早期鉴别最有效的生物标记物[30]（Ⅲ级证据），敏感性和特异性均可达到80%～90%[27]（Ⅲ级证据）。（5）14-3-3蛋白检测：脑脊液14-3-3蛋白水平升高，有助于散发型CJD的诊断，敏感性和特异性分别为90%～100%和84%～96%[31-36]（均Ⅱ级证据）。但脑梗死、脑炎、脑肿瘤和快速进展性AD也可出现假阳性[33-34, 36]（均Ⅱ级证据）。研究提示脑脊液T-tau与14-3-3蛋白联合检测可提高CJD与其他神经系统疾病导致痴呆的鉴别准确率，对CJD敏感度可达96%，特异度达84%[16]（Ⅱ级证据）。当临床拟诊CJD时，应结合EEG[37]、MRI、脑脊液14-3-3蛋白及T-tau蛋白检测结果，以提高CJD诊断的准确性[38-39]（均Ⅱ级证据）。（6）常规项目检测：包括脑脊液压力、细胞计数、糖定量、蛋白定量、蛋白电泳检查和病原学检查等，对排除因中枢神经系统炎症、脱髓鞘疾病、感染性疾病和血管炎性疾病等所致的非AD性痴呆有一定的意义[40]。

【推荐】

当怀疑痴呆的病因为中枢神经系统炎症、血管炎或脱髓鞘疾病等所致时，推荐进行脑脊液常规检查，包括脑脊液压力、细胞计数、糖定量、蛋白定量和（或）蛋白电泳检查等【专家共识】。

对拟诊AD患者推荐进行CSF T-tau、P-tau和Aβ42检测【B级推荐】。

对快速进展的痴呆患者推荐进行CSF 14-3-3蛋白检测【B级推荐】。

二、影像学检查

神经影像学是辅助临床AD、VaD、DLB及FTD诊断和鉴别诊断，排除其他可治疗性痴呆（如手术治疗）非常重要的手段。

1. 头颅CT：AD患者头颅CT可见脑萎缩，分为脑灰质及脑白质萎缩，前者表现为脑回变窄，脑沟加深、增宽，后者表现为侧脑室扩大，脑室角变钝。AD患者的脑萎缩改变主要表现在颞叶、脑白质及脑灰质。颞叶（颞中叶）萎缩表现为颞叶脑沟增多、加深，颞中回变窄，鞍上池和环池增宽、侧脑室颞角扩大；脑白质萎缩显示三脑室和侧脑室体部增宽；脑灰质普遍萎缩，可见双侧大脑半球脑沟增多、加深和脑裂增宽。CT作为结构影像学检查通常用于排除其他可治疗性疾病引起的痴呆，如：肿瘤、血肿及脑积水，这些疾病占痴呆总数1%～10%[41]。CT扫描对VaD诊断辅助作用更为明显。对于未明确的临床痴呆患者神经影像学检查，能帮助发现可逆性原因所致的痴呆。但CT难以准确显示海马结构，诊断痴呆的特异性并不高，临床主要用于疑似痴呆的筛查检查。

【推荐】

CT检查可用于疑似痴呆患者的筛查,鉴别如外科手术等可治疗疾病和血管性疾病引起的痴呆,推荐在没有颅脑MRI或无条件应用颅脑MRI的情况下,CT作为痴呆检查的手段【A级推荐】。

2. 头颅磁共振(MRI):同CT一样,在临床诊疗中有助于发现一些适宜外科手术治疗或因血管性疾病导致的可治疗性痴呆。头颅MRI对痴呆诊断的敏感性及特异性远高于CT,而且MRI还可对脑萎缩作定量分析。(1)阿尔茨海默病(AD):MRI诊断包括结构影像学检查和功能影像学检查。MRI内颞叶结构测量可有效区分轻度AD与认知正常的老年人。在内颞叶结构测量指标中,以海马和内嗅皮质最为重要[42],有研究发现AD最早病变发生于内嗅皮质,然后才累及海马,海马萎缩被认为是AD患者早期特异性标志。67%~100%轻度AD患者有海马萎缩,其对轻中度AD诊断的敏感性及特异性为85%和88%[43-44](Ⅰ级证据)。痴呆患者不伴有MRI上内侧颞叶的萎缩应警惕路易体痴呆(dementia with Lewy bodies, DLB)[45]。MRI功能影像学(functional MRI, fMRI)研究显示AD患者颞顶叶的相对血容量显著降低,其敏感性及特异性与SPECT和PET大致相当。MR波谱(magnetic resonance spectroscopy, MRS)能研究活体特定区域脑组织的代谢状态。应用MRS检测AD患者颞顶叶代谢,显示乙酰天门冬氨酸(NAA)水平下降,肌醇(MI)水平升高。其他类型的痴呆颞顶部NAA水平下降,MI水平正常。此外,AD患者的NAA与胆碱的比值显著变小,AD患者的肌酐(Cr)和胆碱(Cho)研究显示,AD患者MI/Cr及Cho/Cr比值升高,但上述结果正常人群也会有此改变,其诊断及鉴别价值有待进一步研究[46](Ⅱ级证据)。(2)额颞叶痴呆(FTD):MRI上主要表现为额叶和前颞叶显著局限性萎缩,一般双侧对称,但Pick病可以不对称,通常为左侧优势半球萎缩明显,患者的顶叶、颞上回后2/3及枕叶常不受累,表现脑回变窄,两侧侧脑室前角和颞角扩大,其中呈气球样扩大是该病的影像学特征,锥体外系神经核(尤其是豆状核)、岛叶皮质和前胼胝体常受累,MRI T2加权像可显示受累脑皮质和白质区高信号有助于诊断FTD(Ⅰ级证据)[47]。(3)进行性核上性麻痹(progressive superanuclear palsy, PSP):MRI显示中脑和第三脑室周围区域的萎缩为其主要形态学改变,轴位显示中脑形态酷似蝴蝶状;矢状位可见中脑显著萎缩就像尖细的鸟嘴,称"鸟嘴征",如其厚度<14 mm时对诊断PSP有意义(Ⅰ级证据)[48]。(4)血管性痴呆(vascular dementia, VaD):影像学改变包括脑血管病变及相关的脑萎缩。依据血管痴呆的NINDS-AIREN诊断标准,通过影像学特点诊断VaD可靠性为40%~60%(Ⅰ级证据)[49]。对皮质下脑血管病损害MRI较CT敏感性及特异性强,可鉴别AD及VaD。

【推荐】

对疑似痴呆患者尽可能进行结构影像检查。应用MRI(T_1,T_2和FLAIR像)检查能增加诊断及鉴别诊断的特异性,对痴呆疾病随访检查有助于判断疾病预后及药物疗效【A级推荐】。

功能性MRI,磁共振光谱学目前尚不推荐用于痴呆常规诊断检查,但对诊断及鉴别有参考价值【B级推荐】。

3. PET和SPECT:(1)正电子发射断层显像(PET):可用于检测痴呆患者脑血流、葡萄糖代谢的改变,以及多巴胺转运蛋白、5-HT受体、乙酰胆碱酯酶、β-淀粉样蛋白等在脑内的活性。^{18}F-FDG PET是目前最常用于探测人体内葡萄糖代谢的示踪剂,其用于检查痴呆和认知功能障碍患者的价值主要体现在以下4个方面:①用于AD的早期诊断,提高诊断的准确率。一项对395例很可能AD和110例正常对照的研究发现,^{18}F-FDG PET用于诊断轻-中度AD的敏感性和特异性均为93%,诊断极轻度很可能AD的敏感性和特异性分别为84%和93%[50](Ⅱ级证据)。Silverman等[51]汇总分析显示,^{18}F-FDP PET用于诊断病理确诊的AD的敏感性和特异性分别为94%、73%(Ⅱ级证据)。由于研究中使用的AD诊断标准及病例筛选的偏倚,PET的敏感性和特异性报道有差异。一项涉及9项研究的Meta分析显示,PET诊断AD的敏感性和特异性均为86%[52](Ⅰ级证据)。②用于AD与其他类型痴呆的鉴别诊断,^{18}F-FDG PET脑代谢异常与NINCDS-ADRDA临床诊断"很可能AD"的符合率高。^{18}F-FDG PET脑扫描显示不同类型痴呆脑内代谢异常的区域不同,这是各种类型痴呆间鉴别的重要依据[53-56]。Salmon等[57]报道^{18}F-FDG PET用于AD和其他类型痴呆的鉴别有较高的敏感性(94%)、中度特异性(68%)和阳性预测值(65%)(Ⅱ级证据)。③在一定程度上能预测轻度认知功能障碍向痴呆的转换率,及判断痴呆预后。大脑葡萄糖代谢降低预示轻度认知功能障碍的病情恶化[58]。Silverman等[59]对167例MMSE低于24分的病例行PET检查后随访10年发

现，PET 检查异常组有 94% 患者出现认知功能恶化，而阴性组仅 25% 出现认知功能恶化。④指导临床治疗，当^{18}F-FDG PET 检查显示代谢异常与 AD 符合时，可作为开始胆碱酯酶抑制剂治疗的一个指征；^{18}F-FDG PET 还可用于抗痴呆新药疗效判断的指标。Aβ 的 PET 显像是近年来迅速发展起来的特异性诊断 AD 的成像技术。Klunk 等[60]用^{11}C-PIB PET 研究显示，与对照组相比，AD 患者额叶、顶叶、颞叶、部分枕叶和纹状体 PIB 摄取明显增加，与脑内已知可能含有 Aβ 区域一致；而在脑桥、小脑、皮质下白质等已知不含有 Aβ 的区域，PIB 的摄取与对照组相同。Edison 等[61]对 AD 患者行神经心理量表测定、^{11}C-PIB PET 和 FDG PET 检查，其结果显示^{11}C-PIB PET 显像与脑代谢率和认知功能评分间具有良好的相关性。一项关于 AD 和 FTD 的小样本临床研究证实，7 例 AD 患者^{11}C-PIB-PET 脑显像全部阳性，4 例^{11}C-PIB-PET 脑显像阳性的 FTD 患者中 2 例最后证实为 AD，^{11}C-PIB-PET 脑显像有助于 AD 与 FTD 的鉴别[62]（Ⅲ级证据）。2-(1-{6-[(2-[F-18] fluoroethy)(methyl)amino]-2-naphthyl} ethylidene) malononi-trile(^{18}F-FDDNP)能与 Aβ 和神经纤维缠结相结合，可作为诊断 AD 的另一种特异性新型分子探针。Small 等[63]对 25 例 AD 患者、28 例 MCI 患者和 30 例对照组进行 FDDNP PET 研究显示，对照组颞叶、顶叶、扣带回后部及额叶的 FDDNP 摄取明显低于 MCI 患者，而 MCI 患者的摄取又明显低于 AD 患者。^{11}C-PIB 和^{18}F-FDDNP PET 成像能反映活体人脑内 Aβ 和神经原纤维缠结的改变，使 AD 分子病理学诊断成为可能（Ⅱ级证据）。(2)单光子发射计算机断层摄影（SPECT）：能够评估脑的血流灌注。AD 患者主要表现为双侧对称性颞顶叶血流灌注减低。Jagust 等[64]对 70 例经尸检病理证实 AD 研究结果显示，SPECT 诊断 AD 的敏感性和特异性分别为 63% 和 93%（Ⅱ级证据）。对 MCI 患者 5 年随访显示，扣带回前部尾侧及扣带回后部 SPECT 脑显像表现为低灌注的 MCI 患者进展为痴呆的风险增高[65]（Ⅱ级证据）。新近对经病理证实的 25 例 FTD 和 31 例 AD 患者 SPECT 研究显示，额叶脑血流低灌注常见于 FTD 患者，其对 FTD 诊断敏感性和特异性为 80% 和 65%，额叶低灌注不伴顶叶低灌注对诊断 FTD 的特异性增加到 81%；72% FTD 患者无顶叶脑血流改变，而 90% AD 患者有顶叶低灌注，这有助于两者的鉴别诊断[66]（Ⅱ级证据）。以突触前膜多巴胺转运蛋白配体^{123}I-FP-CIT 为示踪剂的 SPECT 脑显像（FP-CIT SPECT），可显示黑质纹状体系统多巴胺转运蛋白活性，FP-CIT SPECT 对诊断 DLB 的敏感性是 88%，特异性是 100%（Ⅱ级证据）。该检测方法可提高 DLB 诊断的准确率，并有助于临床 DLB 与 AD、正常老化间的鉴别[67-68]。但与 PET 相比，SPECT 脑显像分辨率较低，其对痴呆诊断的敏感性和正确性低于 PET 检查。

【推荐】

PET、SPECT 检查均有助于痴呆的诊断和鉴别诊断【B 级推荐】。

对痴呆患者不常规进行 PET 和 SPECT 检查【专家共识】。

对经仔细的临床评估和结构影像学检查后，仍难以明确诊断的痴呆病例，此时进行 PET 检查则可有助于诊断【B 级推荐】。

4. 超声：经颅多普勒超声（transcranial doppler，TCD）能够通过测定颅内血管内血流速度和搏动指数等参数，来反映脑血流和脑血管的状态。但研究显示 VaD 和 AD 患者之间颅内血流速度、搏动指数、脑血管反应性及反映脑微循环功能的脑动静脉转运时间（arterio-venous cerebral transit time，cTT）间差异无统计学意义[69-71]（Ⅱ级证据）。VaD 和 AD 患者全脑血流量（cerebral blood flow，CBF）较正常对照组减慢、全脑循环时间（cerebral circulation time，CCT）延长，VaD 与 AD 两者间 CBF 及 CCT 差异无统计学意义，全脑血容量（cerebral blood volume，CBV）在三组间差异均无统计学意义[72-73]。TCD 的研究结果，有助于证实 VaD 和 AD 等痴呆在发病机制中可能存在共同的血管因素如颅内小血管功能障碍，但尚不能有效鉴别 VaD 和 AD 以及其他痴呆亚型。

【推荐】

鉴别 AD 和 VaD 不推荐用经颅多普勒超声检查【专家共识】。

三、电生理检查

1. 脑电图（electroencephalogram，EEG）检查：对痴呆有一定的诊断价值。AD 患者 90% 可有脑电图异常，表现为 α 节律减慢、不规则、消失或波幅下降。可出现广泛性 θ 波，期间混有 δ 波活动。脑电图检查对于鉴别正常老化与痴呆有一定的实用价值。有研究认为在 AD 临床诊断方面，EEG 敏感性优于神经影像学[40]。Jelic 等[74]对 164 篇文章已发表有金标准诊断的探讨自发脑电图诊断痴呆准确性试验进行荟萃分析证实，试验报道 EEG 对痴呆敏感

性和特异性范围差异很大。因此,EEG作为常规认知功能损害个体的初筛评价方法的证据不足(Ⅰ级证据)。但对特殊类型的痴呆(CJD周期性尖波复合波特征性改变),其诊断的敏感度和特异度可达66%和74%[31](Ⅰ级证据)。此外EEG对大多数痴呆亚型的鉴别诊断也无特异性。定量脑电图(QEEG)技术在痴呆诊疗中的应用一定程度上提高EEG对痴呆的诊断率。但目前除个别前瞻性、大样本研究外,定量EEG在痴呆诊断中的应用多为小样本研究(美国神经精神学会研究委员会关于定量脑电图临床应用价值的总结性报告提示)[75],虽然大多数研究提示定量EEG诊断AD的敏感度和特异度高(分别为72%~98%和81%~100%)[76-77](Ⅱ级证据)。定量EEG和常规EEG的比较研究发现,定量EEG诊断痴呆的敏感度较高,尤其是在痴呆早期和轻度认知功能障碍阶段[78-79]。但值得注意的是,定量EEG的不同参数或不同的技术方法,可能影响痴呆的诊断率。

2. 诱发电位(evoked potential, EP)和事件相关电位(event-related potential, ERP):各种EP和ERP;在痴呆诊断中的应用很不成熟。但是作为检测认知功能损害较为敏感的方法,设计严谨的ERP研究可能通过鉴别认知功能的不同部分从而帮助不同病因痴呆的鉴别诊断;另外,ERP还可用于痴呆治疗的药效评估。闪光视觉诱发电位(visual evoked potential,VEP)中的P2成分和ERP中的P300和N400是痴呆认知功能评价中较常用的检查。P2异常可能对于鉴别AD与其他类型痴呆有较大的帮助。但是AD和健康组的闪光VEP研究发现,个体的AD诊断准确度仅为62%~68%(敏感度分别为80%和60%,特异度分别为53%和75%)[80](Ⅱ级证据),因此对临床医师诊断痴呆的帮助不大。P300也称P3b,是一个在头皮电极上记录到的、出现于刺激发生后300 ms左右的正向电位,由刺激序列中的低概率事件诱发。AD患者通常表现P300潜伏期延长和波幅降低。但是由于P300异常不仅见于AD而且见于其他患者如精神分裂症、抑郁症等,P300的临床意义还有赖于更敏感的检测程序。另外,MCI患者也出现P300延长,而且对于演变为AD有一定的预测作用,但尚须进一步研究证实[40]。N400和P600也在一定程度上反映痴呆患者的认知功能。N400是由各种语言操作任务诱发出的一个头皮记录的负向电位。通常认为可反映语义功能。AD患者可能出现N400潜伏期延长、波幅下降。其程度超过正常老化的范围。P600是一个出现在有意义刺激后约600 ms左右诱发的正向波。N400与P600的界限经常难以区分,与N400类似,P600缺失或降低常见于AD患者[75]。

【推荐】

EEG对于鉴别正常老化和痴呆有较好的辅助诊断价值,其中定量EEG对于鉴别不同种类的痴呆有一定帮助【B级推荐】。

对于疑诊CJD的患者,应该进行EEG检查【B级推荐】。

事件相关电位P300和N400等内源性成分可以作为痴呆认知功能评估的客观手段,对于痴呆程度的判别和预后判断有一定的帮助【B级推荐】。

四、基因检测

现已确认位于14、1、21号染色体上的早老素1(presenilin 1,PS1)基因、早老素2(presenilin 2,PS2)基因、淀粉样前体蛋白(amyloid precursor protein,APP)基因为FAD致病基因。位于17号染色体的微管相关蛋白tau基因[81-82](microtubule-associated protein tau gene, MAPT)和前颗粒体蛋白基因(progranulin gene, PRGN)被证实是额颞叶痴呆(frontotemporal dementia,FTD)的致病基因[83-84]。在家族性FTD患者中存在tau基因突变的约占10%~30%[85-87](Ⅱ级证据)、PRGN基因突变的约占23%[88](Ⅱ级证据)。在家族性克-雅氏病(creutzfeldt-jakob disease,CJD)患者中发现了prion蛋白基因的突变[89]。伴有皮质下梗死和白质脑病的常染色体显性遗传性脑动脉病(cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy,CADASIL)与Notch 3基因多态性相关[90]。位于19号染色体上载脂蛋白Eε4(apolipoprotein E4, ApoE ε4)等位基因作为易感基因,被认为与散发型AD相关联[91]。同时APOEε4基因型也是轻度认知功能障碍(MCI)或非痴呆性认知功能损害(cognitively impaired not demented, CIND)向AD转化的危险因素[92-93]。需要重视的是APOEε4携带者不一定会成为AD患者,且在其他一些痴呆(如FTD)中APOEε4携带率也很高。因此,APOE基因的检测不能作为痴呆诊断的依据。最近发现分拣蛋白相关受体-1(sortilin-related receptor 1 gene,SORL1)基因表达或功能异常也增加晚发型AD患病的风险性[94]。新近针对散发性AD高通量的单核苷酸多态性(single nucleotide polymorphism, SNP)筛查研究提示,一些基因如5-羟色胺受体7

(HTR7)、烟酰胺核苷腺苷酰转移酶 3(NMNAT3)、类阿片样结合蛋白/细胞黏附分子基因(OPCML)基因等可能与晚发型的散发性 AD 的发病相关,有可能成为潜在的候选基因[95]。

对人群中不加选择地进行突变基因的筛查,其阳性率低。而对常染色体显性遗传家族史痴呆患者进行已知基因突变的筛查有助于提供特异性诊断,并能发现早期和临床前期 AD 患者。对有明确家族史,并有明显常染色体显性遗传危险的无临床症状的成人,可以进行基因检测[96]。

【推荐】

有痴呆家族史的痴呆患者应进行基因检测以帮助诊断【A 级推荐】。

基因预测适用于有明确家族史,且有明显的常染色体显性遗传危险的个体【B 级推荐】。

对有痴呆家族史的无症状人群不需要常规进行 APOE 和 SORL1 基因型检测【B 级推荐】。

APOE ε4 基因型检测可用于 MCI/CIND 患者的危险分层,预测其向 AD 转化的风险,并可应用于临床研究中的疗效分析【B 级推荐】。

基因诊断应在专业的、有资质的检测机构进行,以确保检测的准确性【专家共识】。

五、其他检测

组织活检能提供特殊的组织学诊断,例如肝活检对 Wilson 病;皮肤、肌肉活检对 CADASIL、Lafora 小体疾病和线粒体细胞病;CJD 患者扁桃体活检检测朊蛋白。

脑组织活检是痴呆临床诊断过程中最后选择的方法,其原因如下:(1)脑组织活检确诊率不高,有研究报道其确诊率为 57%[97];(2)脑组织活检可能存在严重并发症,包括麻醉意外、出血、感染、甚至死亡。所以决定脑组织活检应取决于对临床风险和获益评估,并取得患者家属同意。脑组织尸体解剖检查对痴呆的确诊有很大的帮助。血管性认知功能损害的确诊也需要有最终的病理诊断。然而,对于怀疑血管性痴呆的病理检查,尚缺乏统一的标准[97]。路易体痴呆的病理改变中,发现路易小体是确诊的必备条件,同时还可见神经原纤维缠结[98-100]。Pick 痴呆的确诊需要大体病理显示额颞叶萎缩及组织病理证实有 Pick 小体及膨胀的 Pick 细胞[101]。混合性痴呆是指具备 2 种单纯性痴呆的病理变化,如 AD、VaD 或其他类型痴呆[102]。

此外,已发现嗅觉黏膜 Tau 病理与 AD 和轻度认知障碍患者具有高度相关性[103-104](Ⅱ级证据)。

【推荐】

对于临床上罕见的痴呆类型,无法用非创伤性技术手段明确诊断时可以采用病理活检【专家共识】。

出现痴呆或认知功能损害,可选择嗅觉黏膜作为活检部位【专家共识】。

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·病例报告·

以腹主动脉瘤为主要表现的白塞病一例

王立 李晓云 孔芳 张奉春

患者男,37 岁,因反复左上腹疼痛 7 个月就诊。7 个月前无明显诱因出现左上腹部疼痛,为间断性钝痛阵发加重,严重时呈刀割样疼痛,向胸部及腰背部放射,伴恶心,无呕吐。不伴有发热、反酸、恶心、大便性状及习惯改变等,发病以来体质量下降 20 kg。当地医院胃镜检查未见明显异常,行腹部 CT 检查提示腹主动脉瘤(图 1,2)。否认胃溃疡、肝炎、结核等病史,否认家族史。近半年来反复口腔溃疡,迁延不愈,下肢曾出现结节样红斑。否认外阴溃疡、眼炎。体格检查:血压 190/110 mm Hg(1 mm Hg = 0.133 kPa),身体消瘦,浅表淋巴结未触及。心、肺查体无异常。左上腹饱满,可触及直径约 5 cm 包块,边界不清,有搏动,听诊可闻及收缩期吹风样杂音。实验室检查:血常规:白细胞 8.51×10^9/L,血红蛋白 120 g/L,血小板 258×10^9/L;尿常规:红细胞 200/高倍视野,蛋白阴性;肝、肾功能:正常。总补体活性(CH50) 74.2×10^3 U/L,C_3 1.56 g/L,C_4 0.30 g/L;免疫球蛋白 G(IgG)18.90 g/L,IgA 9.83 g/L,IgM 1.27 g/L;C 反应蛋白(CRP)20.1 mg/L;红细胞沉降率(ESR)90 mm/1 h;抗中性粒细胞胞质抗体(ANCA)、抗核抗体、自身抗体、抗 ENA 抗体:阴性。针刺试验阳性。考虑"白塞病、腹主动脉瘤"诊断明确,由于目前病情不稳定,需要控制病情后再行手术,否则可能会出现创口愈合困难。给予醋酸泼尼松片 40 mg/d、环磷酰胺 100 mg/d 口服治疗,并积极应用降压药物控制血压。

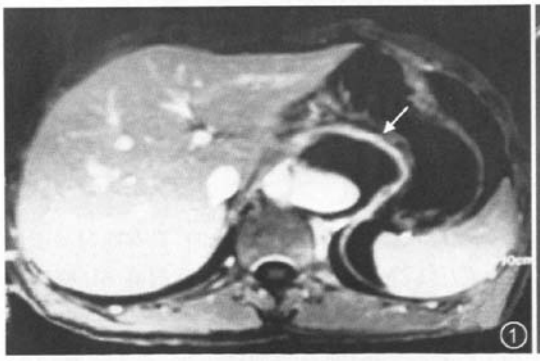

图 1 患者腹部 CT,箭头处示腹主动脉瘤

图 2 患者腹部 CT 的血管重建,箭头处示腹主动脉瘤

讨论:BD 以"三联征——口腔溃疡、外阴溃疡、眼部病变"为最常见的临床表现。该病以 20~40 岁青壮年多见,男性多于女性,且病情多更严重。7%~29% 的患者有血管病变,病变谱较宽,从血栓性、闭塞性、狭窄性到动脉瘤等都能在临床见到。累及大动脉的情况虽不多见,却死亡率极高。该例患者以反复左上腹痛为主要表现,在消化科和血管外科就诊发现腹主动脉瘤,却忽略了其他病史的采集,而在综合了其反复口腔溃疡、结节性红斑、炎性指标升高及针刺反应阳性等特点后,才最终诊断白塞病。治疗方面,白塞病引起的动脉瘤具有生长快、易破裂的倾向,手术不宜等待时间过长。但是,应尽量避免在急性期进行血管手术,而是需积极治疗原发病,从根本上控制病变的进展。否则常常会在动脉重建术后出现血栓、破裂、假性动脉瘤形成等并发症。在原发病病情稳定后,应选择尽快手术。

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中国痴呆与认知障碍诊治指南(四):辅助检查及其选择

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