·循证神经病学·

血管性轻度认知损害诊断标准和筛查技术的循证医学研究

刘霞蔚 时晶 魏明清 田金洲

【摘要】 **研究背景** 血管性轻度认知损害为血管性痴呆的早期阶段，是药物治疗之关键靶点。目前由于国内有关血管性轻度认知损害的诊断标准和筛查技术尚存争议，影响其临床诊断水平的提高，拟通过探讨其临床特征、诊断标准和筛查技术，以为临床提供循证医学参考依据。**方法** 以“vascular mild cognitive impairment OR vascular cognitive impairment no dementia”作为检索式，计算机检索1997年1月–2015年3月美国国立医学图书馆生物医学信息检索系统，获得关于血管性轻度认知损害的指南与共识、临床研究等相关英文文献，参照2004年欧洲神经病协会联盟修订的神经疾病管理指南准备指引进行证据分级。**结果** 最终纳入32篇英文文献，指南与共识3篇，临床研究29篇（Ⅰ类研究11篇、Ⅱ类研究18篇）。其中7篇文献（Ⅰ类2篇、Ⅱ类5篇）报告血管性轻度认知损害的神经心理学特征，显示以信息处理速度减慢和执行功能下降为主要特征；2篇文献报告血管性轻度认知损害的诊断标准（2011年美国心脏协会/美国卒中协会诊断与治疗指南、2014年国际血管性行为与认知障碍学会基于美国精神障碍诊断与统计手册第5版的诊断标准）；15篇文献（Ⅰ类4篇、Ⅱ类11篇）对血管性轻度认知损害的操作性诊断标准进行描述，总结临床常用的6项标准；14篇文献（Ⅰ类4篇、Ⅱ类10篇）对血管性轻度认知损害的神经心理学评价技术进行描述，美国国立神经病学与卒中研究所-加拿大卒中网的5分钟方案与其他测验量表的一致性较高。**结论** 血管性轻度认知损害的神经心理学特征对诊断具有指导意义，国际血管性行为与认知障碍学会公布的诊断标准临床实用性佳，5分钟方案适用于临床快速筛查。

【关键词】 痴呆，血管性； 认知障碍； 神经心理学测验； 诊断； 循证医学

Evidence-based medical research on diagnostic criteria and screening technique of vascular mild cognitive impairment

LIU Xia-wei, SHI Jing, WEI Ming-qing, TIAN Jin-zhou

Department of Neurology, Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing 100700, China

Corresponding author: TIAN Jin-zhou (Email: jztian@hotmail.com)

【**Abstract**】 **Background** Vascular mild cognitive impairment (VaMCI) is the prodromal syndrome of vascular dementia (VaD) and key target for drug treatment. There is controversy over the diagnostic criteria and screening tools of VaMCI, which affects its clinical diagnosis. This paper aims to explore the clinical features, diagnostic criteria and screening technique of VaMCI. **Methods** Taking "vascular mild cognitive impairment OR vascular cognitive impairment no dementia" as retrieval terms, search in PubMed database from January 1997 to March 2015 and screen relevant literatures concerning VaMCI. According to Guidance for the Preparation of Neurological Management Guidelines revised by European Federation of Neurological Societies (EFNS) in 2004, evidence grading was performed on literatures. **Results** A total of 32 literatures in English were selected according to inclusion and exclusion criteria, including 3 guidelines and consensus and 29 clinical studies. Seven literatures (2 on Level Ⅰ, 5 on Level Ⅱ) studied on

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作者单位：100700 北京中医药大学东直门医院脑病科

通讯作者：田金洲（Email：jztian@hotmail.com）

neuropsychological features in VaMCI patients and found reduced processing speed and executive function impairment were main features. Two literatures reported the diagnostic criteria of VaMCI, including VaMCI criteria published by American Heart Association (AHA)/American Stroke Association (ASA) in 2011 and "Diagnostic Criteria for Vascular Cognitive Disorders" published by International Society for Vascular Behavioral and Cognitive Disorders (VASCOG) in 2014. Fifteen literatures (4 on Level Ⅰ, 11 on Level Ⅱ) described the diagnostic criteria of VaMCI used in clinical research, from which 6 operational diagnostic items were extracted. Fourteen literatures (4 on Level Ⅰ, 10 on Level Ⅱ) described neuropsychological assessment tools for VaMCI screening, and found the 5-minute protocol recommended by National Institute of Neurological Disorders and Stroke-Canadian Stroke Network (NINDS-CSN) was being good consistency with other neuropsychological assessment tools. **Conclusions** The neuropsychological features of VaMCI have guiding significance for diagnosis. VASCOG diagnostic criteria for VaMCI is practical in clinical practice, and 5-minute protocol is suitable for clinical rapid screening of VaMCI.

【Key words】 Dementia, vascular; Cognition disorders; Neuropsychological tests; Diagnosis; Evidence-based medicine

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随着人口老龄化的进程,脑卒中已成为国人病残和病死的首要原因[1]。我国为全世界脑卒中发病率最高的国家,脑卒中后认知损害发病率亦呈线性增长,急性脑卒中后3个月有24%~55%患者出现至少一项认知域功能障碍[2-4],至6个月时,有11.60%~72.70%患者发生认知损害,至1年时,仍有69.80%患者存在认知损害[5-6]。脑卒中使痴呆相对危险度升高近3.70倍,在相对年轻的老年人群(61~74岁)中危险度升高得更明显,约6.60倍,而且脑卒中使痴呆的发生提早近10年[7]。脑卒中后认知损害包括血管性轻度认知损害(VaMCI)和血管性痴呆(VaD),研究显示,每年约有10%的血管性轻度认知损害患者进展为血管性痴呆[8-10]。前者是后者早期阶段,二者为一连续疾病谱。因此,血管性轻度认知损害成为预防和治疗血管性痴呆的关键靶点。1995年,Bowler和Hachinski[11]提出"血管性认知损害(VCI)"概念,以涵盖与脑血管病变相关的从轻度认知损害(MCI)到痴呆的整个疾病谱。1997年,Graham等[12]提出"非痴呆型血管性认知损害(VCIND)"概念,以定义与脑血管病变相关但尚未达痴呆诊断标准的认知损害。2003年,O'Brien等[13]提出"血管性轻度认知损害"概念,其含义与非痴呆型血管性认知损害相似,并被美国精神障碍诊断与统计手册第4版(DSM-Ⅳ)认可。2014年,国际血管性行为与认知障碍学会(VASCOG)提出"血管性认知疾病(VCDs)"概念,其含义与血管性认知损害相似。目前,血管性轻度认知损害的诊断标准和筛查工具尚不统一,影响对其临床特征的认识和明确诊断的准确性。鉴于此,本文系统收集并评价关于血管性轻度认知损害临床特征、诊断标准和筛查技术的文献,以为临床诊断与治疗提供循证医学证据。

资料与方法

一、文献筛选

1.纳入标准 (1)研究类型:选择国内外公开发表的关于血管性轻度认知损害的临床研究或指南与共识,仅参考英文文献。(2)研究设计:随机对照试验(RCT)、指南与共识、系统评价(包括Meta分析)。(3)研究对象:受试者年龄≥19岁,性别、种族、受教育程度不限。(4)研究分组:有明确的血管性轻度认知损害分组,而非笼统地包含在"mild cognitive impairment OR MCI"、"vascular cognitive impairment"、"cognitive impairment OR CI"或"cognitive impairment no dementia OR CIND"中。(5)临床研究有明确的纳入与排除标准、明确定义的主要结局,并详细记录基线特征和脱落病例数。

2.排除标准 (1)非人体研究,如动物和细胞等实验研究。(2)非临床研究,如理论探讨、个案报道、经验总结、综述等类型文献。(3)非对照研究,如病例系列研究、病例报告或专家观点。(4)无明确定义的纳入与排除标准,未详细记录受试者基线特征和脱落病例数。

二、文献检索

以"vascular mild cognitive impairment OR

vascular cognitive impairment no dementia”为检索式，计算机检索1997年1月–2015年3月美国国立医学图书馆生物医学信息检索系统（PubMed），获得相关英文文献，并对每篇文献进行质量评价，以判断研究结果的真实性和可靠性。

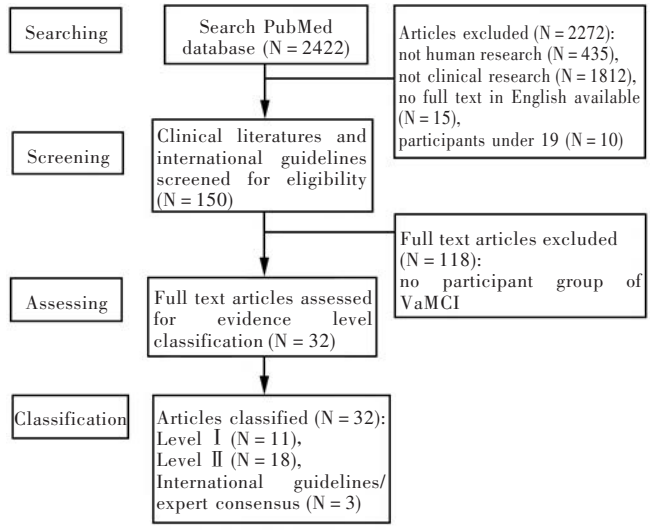
三、文献质量评价与分级

根据筛选出的文献填写证据摘要表，内容包括作者、发表时间、研究样本量、研究对象、研究设计、主要结局指标、主要研究结果和结论、研究标准和参考标准等，并参照2004年欧洲神经病协会联盟（EFNS）修订的神经疾病管理指南准备指引[14]进行证据分级，共计Ⅳ类证据（表1），其中Ⅰ和Ⅱ类证据为高质量文献、Ⅲ和Ⅳ类证据为低质量文献。由两位研究者分别对文献质量进行独立评价，意见不统一时经讨论后裁定。如果一项试验经过补充资料而多次发表，则选择资料最全的一项作为入选者。本研究仅纳入高质量文献。

表1 文献质量评价分级标准

Table 1. Classification criteria for quality evaluation of literatures

Classification	Criteria
Level Ⅰ	Prospective studies in a broad spectrum of persons with the suspected condition (using a "gold standard" for case definition, and applied in a blinded evaluation)
Level Ⅱ	Prospective studies in a narrow spectrum of persons with the suspected condition, or retrospective studies of a broad spectrum of persons with the suspected condition (using a "gold standard" for case definition, and applied in a blinded evaluation)
Level Ⅲ	Retrospective studies (either persons with the suspected condition or controls are of a narrow spectrum, and applied in a blinded evaluation)
Level Ⅳ	Any design not applied in blinded evaluation, or evidence provided by expert opinion alone, or descriptive case series (without controls)



VaMCI，vascular mild cognitive impairment，血管性轻度认知损害

图1 文献筛选流程图

Figure 1 Screening flowchart for literatures.

结　果

一、文献检索及质量评价

经检索共获得英文文献2422篇，按照纳入与排除标准并阅读文题和摘要，最终纳入英文文献32篇，包括指南与共识3篇（无法进行证据分级，可参照Ⅰ类文献处理），临床研究29篇，其中Ⅰ类研究11篇、Ⅱ类研究18篇。文献筛选流程参见图1。

二、研究对象的神经心理学特征

本研究有7篇文献描述血管性轻度认知损害患者神经心理学特征，其中Ⅰ类文献2篇[15-16]、Ⅱ类文献5篇[17-21]，共纳入342例血管性轻度认知损害患者，此7篇文献所设对照组分别为非血管性轻度认知损害（nVMCI）患者、脑小血管病患者、多认知域遗忘型轻度认知损害（aMCI-m）患者和认知功能正常者。结果显示，血管性轻度认知损害患者最严重且最常见的受损神经心理学领域分别为言语功能、执行功能、精神运动速度和（或）信息处理速度、注意力、视空间能力和记忆力（尤其是瞬时记忆），而延迟记忆损害程度相对较轻（表2）。

三、诊断标准

目前，全球已发表的血管性轻度认知损害诊断标准仅2篇，即2011年美国心脏协会（AHA）/美国卒中协会（ASA）发表的诊断与治疗指南[22]和2014年国际血管性行为与认知障碍学会基于DSM-Ⅴ发表的诊断标准[23]，尚未检索到对二者进行诊断效能评价的文献。

本研究有15篇文献描述了血管性轻度认知损害诊断标准，其中Ⅰ类文献4篇[9,15,24-25]、Ⅱ类文献11篇[18-20,26-33]，均未采用上述两项诊断标准，仅为操作性诊断标准，对此15篇文献的诊断条目进行提取，总结较常用于临床研究的操作性诊断标准（表3）：（1）神经心理学测验证实存在认知损害，即1个及以上认知域的确定损害或2个及以上认知域的临界损害（指年龄相匹配常模的第5～10个百分位数或常模均值的1.50～2.00个标准差）。（2）结构影像

表2 血管性轻度认知损害患者认知损害领域之分布范围(共7项研究)[15-21]

Table 2. Cognition domains impaired in VaMCI patients presented by 7 studies[15-21]

Study	No. of subjects	Control	Attention	Psychomotor speed/ processing speed	Visuospatial	Executive function	Language	Orientation	Memory	Other
Meyer, et al[17] (2002)	15	nvMCI	+	–	+	–	+	+	–	–
Nyenhuis, et al[18] (2004)	41	NCI	–	+*	–	–	–	–	Immediate memory*	Depression
Stephens, et al[15] (2004)	92	NCI	–	–	–	+	+	–	+	–
Nordlund, et al[21] (2007)	60	nvMCI	+	+	+	+	–	–	–	–
Sachdev, et al[19] (2009)	45	NCI	–	–	–	+	+	–	Logical memory	–
Sheorajpanday, et al[20] (2013)	35	aMCI-m	–	–	–	–	+	–	Working memory	Matrix reasoning
Salvadori, et al[16] (2015)	146	cSVD	+	–	+	+	+	–	+	–

*most impaired domain。+, positive, 阳性; –, negative, 阴性。nvMCI, non-vascular mild cognitive impairment, 非血管性轻度认知损害; NCI, no cognitive impairment, 非认知损害; aMCI-m, amnesic mild cognitive impairment-multiple domain, 多认知域遗忘型轻度认知损害; cSVD, cerebral small vessel disease, 脑小血管病

表3 血管性轻度认知损害操作性诊断标准(共15项研究)[9,15,18-20,24-33]

Table 3. Operational diagnostic criteria of VaMCI presented by 15 studies[9,15,18-20,24-33]

Study	≥ 1 cognitive impaired domain confirmed by neuropsychological tests	Neuroimage evidence of cerebrovascular disease	Correlation between cerebrovascular disease and cognitive impairment	Normal ability of daily living	Do not meet criteria for dementia	Exclude other reasons causing cognitive impairment
Wentzel, et al[9] (2001)	+	–	+	–	–	–
Ingles, et al[26] (2002)	–	–	+	–	DSM-Ⅲ-R	–
Stephens, et al[15] (2004)	CAMCog < 80	+	–	–	DSM-Ⅲ-R	–
Nyenhuis, et al[18] (2004)	+	+	–	–	DSM-Ⅳ and NINDS-AIREN	–
Borroni, et al[29] (2004)	Norms – 2 SD	–	–	–	DSM-Ⅳ	+
Meyer, et al[31] (2007)	CMC < 42	–	Personal/family history of TIA/stroke/silent stroke	+	DSM-Ⅳ and NINDS-AIREN	–
Sachdev, et al[19] (2009)	+	+	+	–	DSM-Ⅳ	–
Sun, et al[30] (2011)	Norms – 1.50 SD	–	–	+	Not specified	+
Sheorajpanday, et al[20] (2013)	+	+	+	–	DSM-Ⅳ and NINDS-AIREN	–
Yu, et al[24] (2013)	Norms – 10 percentile	–	–	+	DSM-Ⅳ	–
Jiang, et al[27] (2013)	+	+	+	–	Not specified	+
Bella, et al[28] (2013)	–	+	–	–	DSM-Ⅳ	+
Brookes, et al[25] (2015)	scoring ≤1.50 SD of the control population mean on at least four of eight of BMET	+	–	–	–	–
Zhu, et al[32] (2015)	+	+	+	+	–	–
Pasi, et al[33] (2015)	+	+	+	+	DSM-Ⅳ	–

+, positive, 阳性; –, negative, 阴性。CAMCog, Cambridge Cognitive Examination, 剑桥认知评价量表; CMC, combined MMSE and CCSE, 简易智能状态检查量表和认知能力筛查测验合并的测验; BMET, Brief Memory and Executive Test, 简易记忆和执行功能测验; TIA, transient ischemic attack, 短暂性脑缺血发作; DSM, Diagnostic and Statistical Manual of Mental Disorders, 美国精神障碍诊断与统计手册; NINDS-AIREN, National Institute of Neurological Disease and Stroke-Association International pour la Recherche et l'Enseignement en Neurosciences, 美国国立神经病学与卒中研究所-瑞士神经科学研究国际协会

学检查证实存在脑血管病,包括脑白质病变、关键部位梗死灶和多发性腔隙性梗死。(3)脑血管病与认知损害之间具有相关性,如认知损害发生于脑血管病3个月内或Hachinski缺血评分(HIS)≥7分。(4)日常生活活动能力基本正常。(5)不符合痴呆诊断标准。(6)排除导致认知功能障碍的其他原因。上述诊断标准在临床研究中的可操作性较强,但并未对可能导致认知损害的脑血管病严重程度进行严格界定。

四、神经心理学评价技术

目前,仅有1篇文献(Ⅰ类证据)对血管性轻度认知损害神经心理学评价技术作出推荐,2006年由

美国国立神经病学与卒中研究所-加拿大卒中网(NINDS-CSN)发表[34],包括3种神经心理学评价方案,即60、30和5分钟方案,三者外部一致性分别为0.88、0.88和0.86,内部一致性分别为0.90、0.83和0.75[35]。Kennedy等[36]在7199例45岁以上认知功能正常的无脑卒中成人受试者中对5分钟方案进行验证(Ⅰ类证据),其结果显示:5分钟方案总评分与年龄和心血管风险呈负相关($P=0.000$),与受教育程度、6条目筛选表(SIS)、单词列表学习测验(WLL)、动物范畴词语流畅性测验(AFT)呈正相关($P=0.000$)。但未检索到关于上述3种方案诊断效能的研究。

本研究有14篇文献对血管性轻度认知损害所采用的神经心理学测验量表进行描述[9,17,19-20,24-33],其中Ⅰ类文献4篇[9,17,24-25]、Ⅱ类文献10篇[19-20,26-33]。其中1篇文献[24]采用60分钟方案对急性缺血性卒中3个月后患者进行评价,其血管性轻度认知损害阳性率约为49.90%,但该项试验未对其诊断效能进行评价。其余13篇文献均对整体认知水平进行评价,包括简易智能状态检查量表(MMSE)8篇、蒙特利尔认知评价量表(MoCA)3篇、韦氏成人智力量表(WAIS)/韦氏记忆量表(WMS)3篇、临床痴呆评价量表(CDR)2篇、认知能力筛查测验(CCSE)2篇、剑桥认知评价量表(CAMCog)/剑桥老年精神障碍检查(CAMDEX)2篇。其中,3篇文献进行日常生活活动能力检查[日常生活活动能力量表(ADL)/工具性日常生活活动能力量表(IADL)];4篇行词语流畅性测验[受控口语词语联想测验(COWAT)2篇、动物命名测验(ANT)2篇、Boston命名测验(BNT)2篇];5篇行抑郁症状评价[老年抑郁量表(GDS)3篇、汉密尔顿抑郁量表(HAMD)2篇];2篇行视空间能力测验[Rey-Osterrieth复杂图形测验(ROCFT)];4篇对患者注意力、反应速度和执行功能进行测验[连线测验3篇、数字警觉测验(DVT)1篇、简易记忆和执行功能测验(BMET)1篇];1篇行额叶功能评价[Stroop色词测验(SCWT)];3篇进行记忆力测验[数字广度测验(DS)2篇、故事回忆测验(SRT)1篇、Benton视觉保持测验(BVRT)/Buschke线索回忆测验(BCRT)1篇、Rey听觉-词汇学习测验(RAVLT)1篇]。

本研究纳入1篇对BMET量表诊断效能进行评价的文献[25],其结果显示:当BMET评分临界值为13分时,其区分脑小血管病性认知损害的灵敏度为93%、特异度为76%,且诊断准确性[受试者工作特征(ROC)曲线下面积(AUC)=0.940]高于MMSE量表(AUC=0.700)和MoCA量表(AUC=0.770)。其余文献均未对神经心理学评价技术筛查血管性轻度认知损害的敏感性和特异性进行评价。

讨 论

相较于颅内大血管病变,脑小血管病可能是导致血管性轻度认知损害的常见病理学因素(Ⅱ类证据)[37]。其常见病理改变为腔隙性梗死和脑白质病变,导致的认知损害可归因于皮质-皮质下环路受损,主要影响信息处理速度、复杂注意力和执行功能[38]。本研究结果显示,血管性轻度认知损害主要表现为执行功能、精神运动速度和(或)信息处理速度、视空间能力和言语功能障碍。Vasquez和Zakzanis[39]对27项针对血管性轻度认知损害与正常对照、20项针对血管性轻度认知损害与非血管性轻度认知损害的研究进行Meta分析,结果显示:与正常对照组相比,血管性轻度认知损害组患者信息处理速度、整体功能、延迟记忆和瞬时记忆显著受损;与非血管性轻度认知损害组相比,血管性轻度认知损害组患者信息处理速度和执行功能显著受损,与本研究结果相似。但目前并无研究显示血管性轻度认知损害与非血管性轻度认知损害在记忆或非记忆认知域存在差异(Ⅰ和Ⅱ类证据)[21,40]。

VASCOG公布的标准将血管性轻度认知损害诊断临界值由AHA/ASA标准中对照组1.00~1.50个标准差扩大至1~2个标准差,并列举3种支持证据,进一步细化血管性轻度认知损害的排除标准。同时,VASCOG标准还对脑血管病程度和类型给出具体定义:(1)1个以上颅内大血管病变。(2)2个以上脑干以外腔隙性梗死灶。(3)单个腔隙性梗死灶伴轻度脑白质病变,或关键部位单个腔隙性梗死灶。(4)不伴梗死灶的单纯脑白质病变(由于脑白质病变影响因素众多,不宜在诊断标准中规定其发生范围)。(5)广泛性微出血灶,不包括硬膜下出血。目前尚无对上述两项标准之诊断效能进行评价的研究。VASCOG标准放宽了神经心理学测验评分范围,并对神经影像学严重程度给出了较有操作性的规定,适用于临床。

目前,适用于血管性轻度认知损害的神经心理学筛查工具尚无统一标准,各项临床试验采用的量表多样,根据血管性轻度认知损害的神经心理学特征,其筛查工具至少应包含记忆力、视空间能力、言

语功能和执行功能测验。NINDS-CSN的5分钟方案是从MoCA量表中筛选出部分测验项目组合而成，适用于快速筛查、大规模流行病学调查和电话筛查。由于其简便易行，更适用于临床操作。该方案包含延迟记忆和瞬时记忆、定向力及言语功能测验，但缺乏执行功能测验，因此在实际操作中，如果有条件，可以配合计时的执行功能测验如连线测验。5分钟方案在血管性认知损害患者中的诊断准确性较高（AUC=0.780，Ⅱ类证据）[41]，但目前仍缺乏其对血管性轻度认知损害诊断效能的评价。

日常生活活动能力是区分血管性轻度认知损害和血管性痴呆的重要因素，较常用的测验量表为ADL量表，包括较复杂的工具性日常生活活动能力和基本日常生活活动能力两部分，轻度认知损害患者通常表现为工具性日常生活活动能力轻度损害，而基本日常生活活动能力相对保留。简文佳等[42]对轻度认知损害、痴呆和认知功能正常者的14项ADL评分进行比较，其区分轻度认知损害与痴呆的临界值为16分（灵敏度90%、特异度93%，Ⅱ类证据），但并未对血管性轻度认知损害进行单独分析。

本研究存在以下不足：（1）仅检索PubMed数据库。（2）检索式的设置相对简单，由于目前对血管性轻度认知损害的名称尚未统一，可能忽略一些针对血管性轻度认知损害但命名不同的文献，造成选择偏倚，尚待扩大检索范围进行更深入的研究。

结　论

目前，针对血管性轻度认知损害的研究相对较少，不同研究之间纳入标准和诊断标准差异较大，较难通过系统评价获得相对稳定、可靠的结论。本研究通过对筛选的文献进行循证医学证据评价，发现血管性轻度认知损害主要表现为执行功能、精神运动速度和（或）信息处理速度、视空间能力和言语功能受损；VASCOG标准具有良好的操作性，适用于临床，但尚待进一步验证其诊断效能；NINDS-CSN的5分钟方案简便、易行，适用于临床快速筛查，尚待进一步研究其敏感性和特异性。

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