·阿尔茨海默病及相关痴呆·

阿尔茨海默病伴脑白质病变患者认知功能及精神行为特征

陈媛 张森 王艳 张惠红 周玉颖 李攀

【摘要】 目的 总结阿尔茨海默病伴脑白质病变(WML)患者的认知功能和精神行为特点。**方法** 纳入2010年1月至2020年12月天津市环湖医院收治的共58例阿尔茨海默病患者,采用简易智能状态检查量表(MMSE)和蒙特利尔认知评价量表(MoCA)评价认知功能、日常生活活动能力量表(ADL)评价日常生活活动能力、神经精神科问卷(NPI)评价神经精神行为、汉密尔顿抑郁量表21项(HAMD-21)评价抑郁症状、临床痴呆评价量表(CDR)评价痴呆程度,行头部MRI检查,通过脑白质高信号[WMH,包括脑室旁白质高信号(PWMH)和脑深部白质高信号(DWMH)]对脑白质病变进行半定量视觉评分。**结果** (1)WML组患者高血压比例($\chi^2=4.665$, $P=0.031$)、NPI评分($Z=1.987$, $P=0.047$)和CDR评分($Z=2.069$, $P=0.039$)高于,MMSE评分($t=2.927$, $P=0.005$)和MoCA评分($t=3.394$, $P=0.001$)低于无WML组,其中,WML组MMSE量表中注意力和计算力($Z=2.234$, $P=0.025$)、回忆能力($Z=2.792$, $P=0.005$)、命名($Z=2.382$, $P=0.017$)、复述($Z=2.685$, $P=0.007$)等认知域评分较低, NPI量表中妄想(Fisher确切概率法:$P=0.046$)、抑郁/心境恶劣($\chi^2=4.376$, $P=0.036$)、情感淡漠/漠不关心($\chi^2=4.063$, $P=0.044$)发生率较高。(2)中至重度WML组高血压比例($\chi^2=11.195$, $P=0.001$)和低密度脂蛋白胆固醇($t=2.573$, $P=0.013$)以及ADL评分($Z=3.269$, $P=0.001$)、NPI评分($Z=3.439$, $P=0.001$)和CDR评分($t=2.740$, $P=0.006$)高于,MMSE评分($t=3.686$, $P=0.001$)和MoCA评分($t=5.225$, $P=0.000$)低于无或轻度WML组。(3)轻度、中度与重度痴呆组同型半胱氨酸(Hcy;$F=6.291$, $P=0.003$)、高血压比例($\chi^2=10.716$, $P=0.005$)、伴脑白质病变比例($\chi^2=8.100$, $P=0.017$)、Fazekas总评分($H=13.658$, $P=0.001$)、脑室旁白质高信号Fazekas评分($H=6.540$, $P=0.038$)、脑深部白质高信号Fazekas评分($H=21.550$, $P=0.000$)差异均有统计学意义,其中重度痴呆组高血压比例($\chi^2=6.702$, $P=0.010$;Fisher确切概率法:$P=0.006$)、Hcy($P=0.039$, 0.001)、Fazekas总评分($Z=2.898$, $P=0.004$;$Z=3.223$, $P=0.001$)、脑深部白质高信号Fazekas评分($Z=2.807$, $P=0.005$;$Z=4.144$, $P=0.000$)均高于中度痴呆组和轻度痴呆组,仅伴脑白质病变比例高于轻度痴呆组(Fisher确切概率法:$P=0.008$),脑室旁白质高信号Fazekas评分高于中度痴呆组($Z=2.567$, $P=0.010$),中度痴呆组脑深部白质高信号Fazekas评分亦高于轻度痴呆组($Z=2.950$, $P=0.003$)。(4)合并高血压组Fazekas总评分($Z=3.284$, $P=0.001$)和脑深部白质高信号Fazekas评分($Z=4.083$, $P=0.000$)高于不合并高血压组。**结论** 脑白质病变程度与阿尔茨海默病患者认知功能和神经精神行为密切相关,可以作为阿尔茨海默病进展的观察指标,应重视早期脑白质病变危险因素的筛查和预防。

【关键词】 阿尔茨海默病; 大脑小血管疾病; 认知障碍; 神经心理学测验

Characteristics of cognitive and neuropsychiatric behavioral features of Alzheimer´s disease with white matter lesion

CHEN Yuan, ZHANG Miao, WANG Yan, ZHANG Hui-hong, ZHOU Yu-ying, LI Pan

Department of Neurology, Tianjin Huanhu Hospital; Tianjin Key Laboratory of Cerebral Vascular and Neurodegenerative Diseases, Tianjin 300350, China

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作者单位:300050 天津市环湖医院神经内科 天津市脑血管与神经变性重点实验室

通讯作者:周玉颖,Email:qiying789@sina.cn;李攀,Email:doc_panpan@163.com

Corresponding authors: ZHOU Yu-ying (Email: qiying789@sina.cn); LI Pan (Email: doc_panpan@163.com)

【Abstract】 Objective To study the characteristics of cognitive and neuropsychiatric behavioral features of Alzheimer's disease (AD) with white matter lesion (WML). **Methods** A total of 58 cases of AD patients were reruited from January 2010 to December 2020. The Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) were used to evaluate the degree of cognitive impairments. Activities of Daily Living Scale (ADL) was used to evaluate the abilities of daily living. Neuropsychiatric Inventory (NPI) was used to evaluate behavioral and psychological symptoms. The Hamilton Depression Rating Scale 21-Items (HAMD-21) was used to evaluate the mental or emotional state. Clinical Dementia Rating Scale (CDR) was used to evaluate the dementia severity. The Fazekas scale was utilized to assess the severity of periventricular white matter hyperintensities (PWMH) and deep white matter hyperintensities (DWMH). **Results** 1) The distribution frequency of hypertension (χ^2 = 4.665, P = 0.031), NPI score (Z = 1.987, P = 0.047), CDR score (Z = 2.069, P = 0.039), MMSE score (t = 2.927, P = 0.005) and MoCA score (t = 3.394, P = 0.001) in WML group were significantly different than those in non-WML group. Among which, attention and calculation ability (Z = 2.234, P = 0.025), recall ability (Z = 2.792, P = 0.005), naming ability (Z = 2.382, P = 0.017), retelling ability (Z = 2.685, P = 0.007) were lower than those in non-WML group. The incidence of delusion (Fisher's exact probability: P = 0.046), depression/dysthymia (χ^2 = 4.376, P = 0.036), apathy/indifference (χ^2 = 4.063, P = 0.044) in WML group were significantly higher than those in non-WML group. 2) The distribution frequency of hypertension (χ^2 = 11.195, P = 0.001), low-density lipoprotein cholesterol (LDL-C; t = 2.573, P = 0.013), ADL score (Z = 3.269, P = 0.001), NPI score (Z = 3.439, P = 0.001) and CDR score (t = 2.740, P = 0.006) in moderate to severe WML group were higher than those in mild WML group. MMSE score (t = 3.686, P = 0.001) and MoCA score (t = 5.225, P = 0.000) were lower than those in without or mild WML group. 3) Homocysteine (Hcy; F = 6.291, P = 0.003), distribution frequency of hypertension (χ^2 = 10.716, P = 0.005), distribution frequency of WML (χ^2 = 8.100, P = 0.017), total Fazekas scores (H = 13.658, P = 0.001), Fazekas score of PWMH (H = 6.540, P = 0.038) and Fazekas score of DWMH (H = 21.550, P = 0.000) were statistically significant. While distribution frequency of hypertension (χ^2 = 6.702, P = 0.010; Fisher's exact probability: P = 0.006), Hcy (P = 0.039, 0.001), Fazekas total scores (Z = 2.898, P = 0.004; Z = 3.223, P = 0.001) and Fazekas score of DWMH (Z = 2.807, P = 0.005; Z = 4.144, P = 0.000) in severe dementia group were higher than those in moderate and mild dementia group, and only the distribution frequency of WML was higher than that in mild dementia group (Fisher's exact probability: P = 0.008), Fazekas score of PWMH was higher than that in moderate dementia group (Z = 2.567, P = 0.010), and Fazekas score of DWMH in moderate dementia group was higher than that in mild dementia group (Z = 2.950, P = 0.003). 4) The total Fazekas scores (Z = 3.284, P = 0.001) and DWMH scores (Z = 4.083, P = 0.000) in AD patients with hypertension were significantly higher than those in AD patients without hypertension. **Conclusions** The degree of WML was closely related to cognitive function and neuropsychiatric behavioral symptoms of AD patients, which can be used as an observation index for the development of AD. Therefore, we should pay attention to early screening and prevention of WML related risk factors.

【Key words】 Alzheimer disease; Cerebral small vessel diseases; Cognition disorders; Neuropsychological tests

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阿尔茨海默病是一种以进行性认知功能障碍和精神行为异常为主要临床特征的神经变性病，是最常见的痴呆类型[1]。血管性因素参与阿尔茨海默病的发生发展，其在阿尔茨海默病发病机制中的作用越来越受到重视。阿尔茨海默病的血管病变以颅内微血管为主[2]，可能与认知功能障碍和精神行为异常相关[3]。脑白质病变（WML）亦称脑白质疏松症（LA），属于神经影像学概念，以脑白质完整性破坏或脱髓鞘改变为主要病理学表现，头部MRI呈现脑白质高信号（WMH）[4]。根据病变部位分为脑室旁白质高信号（PWMH）和脑深部白质高信号（DWMH）。业已证实，脑白质病变与认知功能下降相关[5-6]。鉴于此，本研究通过对阿尔茨海默病患者脑白质病变进行分类评估，系统分析脑白质病变与阿尔茨海默病患者认知功能和精神行为之间的关系，以期深入探讨脑白质病变对阿尔茨海默病认知

功能和精神行为的影响。

资料与方法

一、临床资料

1.纳入标准 (1)均符合2011年美国国家老龄化研究所-阿尔茨海默病学会(NIA-AA)有阿尔茨海默病生物学标志物的很可能的(probable)阿尔茨海默病诊断标准[7]。(2)由至少2位具备丰富临床经验的副主任及以上级别的神经内科专科医师诊断为很可能的阿尔茨海默病。(3)均经^{18}F-脱氧葡萄糖(^{18}F-FDG)PET显像符合阿尔茨海默病影像学改变,即以后颞顶联合皮质和后扣带回为主的葡萄糖代谢降低[8]。(4)均有可靠照料者陪伴。(5)患者或其法定监护人均对本研究检查项目知情并签署知情同意书。

2.排除标准 (1)存在其他类型痴呆,如血管性痴呆(VaD)、额颞叶痴呆(FTD)、路易体痴呆(DLB)等,或者存在可能引起其他痴呆或认知功能障碍的神经系统疾病或严重内科系统疾病,如颅脑创伤(TBI)、脑肿瘤、癫痫、中枢神经系统炎症、中枢神经系统脱髓鞘疾病、正常颅压脑积水(NPH)、严重肝肾功能障碍、严重贫血、甲状腺功能减退症、维生素B_{12}缺乏症等。(2)存在辐射损伤、一氧化碳中毒、多发性硬化(MS)、血管炎或脑白质营养不良导致的脑白质高信号或其他类型脑白质病变。(3)有明确的脑血管病病史,Hachinski缺血评分(HIS)>4。(4)有明确的精神分裂症、严重抑郁症等精神疾病病史,或者明确的药物、酒精滥用史。(5)伴严重视力和听力障碍、意识障碍、严重失语等无法完成神经心理学测验。(6)生物学标志物检测提示其他神经系统退行性变。

3.一般资料 选择2010年1月至2020年12月在天津市环湖医院神经内科痴呆诊疗中心就诊的阿尔茨海默病患者58例,男性26例,女性32例;年龄51~80岁,平均(63.43±7.20)岁;发病年龄47~76岁,平均(60.12±7.02)岁;受教育程度1~16年,平均为(10.62±3.41)年;体重指数(BMI)14.50~37.10 kg/m^2,平均为(23.00±3.67) kg/m^2;既往合并高血压24例(41.38%)、冠心病10例(17.24%)、糖尿病15例(25.86%),有痴呆家族史18例(31.03%),吸烟史19例(32.76%)、饮酒史15例(25.86%)。

二、研究方法

1.实验室检查 所有患者于静脉血采集前一晚20:00后禁食,次日晨起空腹采集肘静脉血4~5 ml,测定空腹血糖、总胆固醇(TC)、甘油三酯(TG)、低密度脂蛋白胆固醇(LDL-C)、高密度脂蛋白胆固醇(HDL-C)、铁蛋白(SF)、维生素B_{12}、叶酸、同型半胱氨酸(Hcy)、甲状腺功能试验等。

2.神经心理学测验 采用盲法由1位经过规范化培训并熟练操作且对患者临床和影像学检查均不知情的神经内科医师,对患者进行神经心理学测验,并通过访谈可靠的照料者评估患者痴呆行为和精神症状(BPSD)。(1)认知功能评估:采用简易智能状态检查量表(MMSE)[9]和蒙特利尔认知评价量表(MoCA)[10],总评分均为30。MMSE量表包括定向力(10分)、记忆力(3分)、注意力和计算力(5分)、回忆能力(3分)、语言(8分)、视空间(1分)共6个方面10项内容,评分21~26为轻度痴呆、10~20为中度痴呆、<10为重度痴呆。MoCA评分<26为存在认知功能障碍,对于受教育程度≤12年的患者,总评分加1用于校正受教育程度偏倚。(2)日常生活活动能力评估:采用日常生活活动能力量表(ADL)[11],总评分为80,包括基本日常活动能力量表(BADL)11项和工具性日常活动能力量表(IADL)9项,评分越高,其日常生活活动能力越差。(3)抑郁评估:采用汉密尔顿抑郁量表21项(HAMD-21)[12],评分7~16为轻度抑郁、17~23为中度抑郁、≥24为重度抑郁。(4)神经精神行为评估:采用神经精神科问卷(NPI)[13]对可靠照料者进行访谈,包括妄想、幻觉、激越/攻击性、抑郁/心境恶劣、焦虑、情绪高涨/欣快、情感淡漠/漠不关心、脱抑制、易激惹/情绪不稳、异常运动行为、睡眠/夜间行为、食欲和进食障碍12项症状,分别根据发作频率、严重程度、引起照料者的苦恼程度进行评分,总评分为144,评分越高、神经精神行为异常越严重。(5)痴呆评估:采用临床痴呆评价量表(CDR)[14],正常为0、可疑痴呆为0.5、轻度痴呆为1、中度痴呆为2、重度痴呆为3。

3.脑白质病变半定量视觉评分 所有患者均在痴呆诊疗中心行头部MRI检查,采用德国Seimens公司生产的Skyra 3.0T超导型MRI扫描仪,20通道头部线圈,分别扫描3个截面即冠状位、横断面和矢状位,扫描序列包括T_1WI、T_2WI、FLAIR成像和DWI。脑白质病变半定量视觉评分主要通过Fazekas评分(评分为0~6)[15]在FLAIR成像上实施,采用盲法由同一位影像科医师在不知情临床数据的情况下,分别对脑室旁白质高信号和脑深部白

表1 WML组与无WML组患者临床资料和神经心理学测验评分的比较

Table 1. Comparison of clinical data and neuropsychological scores between WML group and non-WML group

观察指标	无WML组（n=16）	WML组（n=42）	统计量值	*P*值
性别[例(%)]			0.239	0.625
男性	8/16	18(42.86)		
女性	8/16	24(57.14)		
年龄($\bar{x}\pm s$,岁)	62.88±7.26	63.64±7.26	0.360	0.720
发病年龄($\bar{x}\pm s$,岁)	60.75±6.98	59.88±7.10	0.418	0.677
受教育程度($\bar{x}\pm s$,年)	10.44±4.02	10.69±3.20	0.251	0.803
BMI($\bar{x}\pm s$,kg/m^2)	22.15±4.06	23.33±3.50	1.098	0.277
高血压[例(%)]	3/16	21(50.00)	4.665	0.031
冠心病[例(%)]	1/16	9(21.43)	—	0.256
糖尿病[例(%)]	5/16	10(23.81)	—	0.738
痴呆家族史[例(%)]	5/16	13(30.95)	—	1.000
吸烟史[例(%)]	7/16	12(28.57)	1.212	0.271
饮酒史[例(%)]	7/16	8(19.05)	—	0.091
空腹血糖($\bar{x}\pm s$,mmol/L)	5.62±1.18	6.03±1.36	1.072	0.288
TC($\bar{x}\pm s$,mmol/L)	5.09±1.07	5.34±1.28	0.685	0.496
TG($\bar{x}\pm s$,mmol/L)	1.32±0.59	1.39±0.48	0.441	0.661
LDL-C($\bar{x}\pm s$,mmol/L)	3.16±0.76	3.52±0.85	1.494	0.141
HDL-C($\bar{x}\pm s$,mmol/L)	1.43±0.41	1.45±0.32	0.261	0.795
Hcy($\bar{x}\pm s$,μmol/L)	12.30±5.26	14.14±5.48	1.160	0.251
MMSE($\bar{x}\pm s$)	17.88±5.76	12.17±6.93	2.927	0.005
MoCA($\bar{x}\pm s$)	13.50±6.23	7.88±5.40	3.394	0.001
ADL[$M(P_{25},P_{75})$]	27.50 (21.25,34.75)	30.00 (24.00,40.00)	1.458	0.145
HAMD-21[$M(P_{25},P_{75})$]	6.00 (3.25, 9.50)	5.00 (4.00, 9.00)	0.210	0.834
NPI[$M(P_{25},P_{75})$]	4.50 (2.25,11.25)	11.00 (4.00,16.25)	1.987	0.047
CDR[$M(P_{25},P_{75})$]	1.00 (0.50, 2.00)	2.00 (1.00, 2.00)	2.069	0.039

—, Fisher's exact probability, Fisher确切概率法。χ^2 test for comparison of sex, hypertension and smoking, two-independent-sample *t* test for comparison of age, onset age, education, BMI, blood glucose, TC, TG, LDL-C, HDL-C, Hcy, MMSE and MoCA, and Mann-Whitney *U* test for comparison of others,性别、高血压和吸烟史的比较行χ^2检验,年龄、发病年龄、受教育程度、BMI、空腹血糖、TC、TG、LDL-C、HDL-C、Hcy、MMSE评分和MoCA评分的比较行两独立样本的*t*检验,其余各项指标的比较行Mann-Whitney *U*检验。WML, white matter lesion,脑白质病变;BMI, body mass index,体重指数;TC, total cholesterol,总胆固醇;TG, triglyceride,甘油三酯;LDL-C, low-density lipoprotein cholesterol,低密度脂蛋白胆固醇;HDL-C, high-density lipoprotein cholesterol,高密度脂蛋白胆固醇;Hcy, homocysteine,同型半胱氨酸;MMSE, Mini-Mental State Examination,简易智能状态检查量表;MoCA, Montreal Cognitive Assessment,蒙特利尔认知评价量表;ADL, Activities of Daily Living Scale,日常生活活动能力量表;HAMD-21, Hamilton Depression Rating Scale 21-Items,汉密尔顿抑郁量表21项;NPI, Neuropsychiatric Inventory,神经精神科问卷;CDR, Clinical Dementia Rating Scale,临床痴呆评价量表

质高信号进行评分(各评分为0~3),脑室旁白质高信号,0为无病灶,1为帽状或铅笔样薄层局灶性病灶,2为病灶呈光滑的晕圈,3为病灶弥漫累及整个侧脑室前角、后角及体部,伴或不伴U型纤维受累;脑深部白质高信号,0为无病灶,1为斑点状病灶,2为病灶开始融合,3为病灶大面积不规则融合,其中斑点状指病灶最大直径<5 mm,不规则融合指病灶最大直径>10 mm。两部分评分之和即为总评分,0为无脑白质病变,1~2为轻度脑白质病变,3~4为中度脑白质病变,5~6为重度脑白质病变。同时由另一位高年资影像科医师复核其结果,以确保客观性和准确性。

4.统计分析方法 采用SPSS 26.0统计软件进行数据处理与分析。计数资料以相对数构成比(%)或率(%)表示,采用χ^2检验或Fisher确切概率法。正态性检验采用Shapiro-Wilk检验。呈正态分布的计量资料以均数±标准差($\bar{x}\pm s$)表示,两组间比较采用两独立样本的*t*检验;多组间比较采用单因素方差分析,两两比较行LSD-*t*检验。呈非正态分布的计量资料以中位数和四分位数间距[$M(P_{25},P_{75})$]表示,两组间比较采用Mann-Whitney *U*检验;多组间比较采用Kruskal-Wallis检验(*H*检验),两两比较行Mann-Whitney *U*检验。以$P\leq 0.05$为差异具有统计学意义。

结 果

本组58例患者根据Fazekas评分分为阿尔茨海默病伴脑白质病变组(WML组,42例)和不伴脑白质病变组(无WML组,16例)。与无WML组相比,WML组高血压患者比例($P=0.031$)以及NPI评分($P=0.047$)和CDR评分($P=0.039$)较高,MMSE评分($P=0.005$)和MoCA评分($P=0.001$)较低,而两组性别、年龄、发病年龄、受教育程度、体重指数、冠心病和糖尿病比例、痴呆家族史比例、吸烟史和饮酒史比例、空腹血糖、TC、TG、LDL-C、HDL-C、Hcy、ADL和HAMD-21评分差异无统计学意义(均$P>0.05$,表1)。

对两组患者MMSE量表各项分评分进行比较,与无WML组相比,WML组注意力和计算力($P=0.025$)、回忆能力($P=0.005$)、命名($P=0.017$)和复述($P=0.007$)评分较低,其余各项分评分组间差异无统计学意义(均$P>0.05$,表2)。

对两组患者精神行为异常发生率进行比较,与

表2 WML组与无WML组患者MMSE量表各项分评分的比较[$M(P_{25},P_{75})$]

Table 2. Comparison of subitems score of MMSE scale between WML and non-WML groups [$M\ (P_{25},\ P_{75})$]

观察指标	无WML组（n=16）	WML组（n=42）	Z值	P值
定向力	5.50(3.00,7.75)	3.00(2.00,5.00)	1.779	0.075
记忆力	3.00(2.00,3.00)	3.00(1.50,3.00)	0.999	0.318
注意力和计算力	2.00(1.00,4.00)	1.00(0.00,2.00)	2.234	0.025
回忆能力	1.00(0.00,2.00)	0.00(0.00,0.00)	2.792	0.005
命名	2.00(2.00,2.00)	2.00(1.00,2.00)	2.382	0.017
复述	1.00(0.00,1.00)	0.00(0.00,0.00)	2.685	0.007
完成命令	2.50(2.00,3.00)	2.00(1.00,3.00)	1.529	0.126
阅读	1.00(1.00,1.00)	1.00(0.00,1.00)	1.906	0.057
书写	1.00(0.00,1.00)	0.00(0.00,1.00)	1.585	0.113
视空间能力	0.00(0.00,1.00)	0.00(0.00,0.00)	1.886	0.059

WML,white matter lesion,脑白质病变

表3 WML组与无WML组患者精神行为异常发生率的比较[例(%)]

Table 3. Comparison of the incidence of abnormal mental behavior between WML and non-WML groups [case (%)]

观察指标	无WML组（n=16）	WML组（n=42）	χ^2值	P值
妄想	1/16	14(33.33)	—	0.046
幻觉	2/16	9(21.43)	—	0.710
激越/攻击性	3/16	14(33.33)	—	0.347
抑郁/心境恶劣	5/16	26(61.90)	4.376	0.036
焦虑	7/16	20(47.62)	0.070	0.792
情绪高涨/欣快	1/16	4(9.52)	—	1.000
情感淡漠/漠不关心	6/16	28(66.67)	4.063	0.044
脱抑制	1/16	5(11.90)	—	1.000
易激惹/情绪不稳	9/16	23(54.76)	0.010	0.919
异常运动行为	5/16	17(40.48)	0.419	0.517
睡眠/夜间行为	8/16	12(28.57)	2.355	0.125
食欲和进食障碍	4/16	6(14.29)	—	0.439

—,Fisher's exact probability,Fisher确切概率法

无WML组相比,WML组患者妄想(Fisher确切概率法:$P=0.046$)、抑郁/心境恶劣($P=0.036$)、情感淡漠/漠不关心($P=0.044$)发生率较高,其余各项发生率组间差异无统计学意义(均$P>0.05$,表3)。

本组58例患者根据Fazekas评分分为无脑白质病变(评分为0),轻度脑白质病变(评分为1~2),中度脑白质病变(评分为3~4),重度脑白质病变(评分为5~6)。Fazekas总评分为0~2者32例,作为无或轻度脑白质病变组(无或轻度WML组);Fazekas总评分3~6者26例,作为中至重度脑白质病变组(中至重度WML组)。与无或轻度WML组相比,中至重度WML组高血压比例($P=0.001$)和LDL-C($P=0.013$)以及ADL评分($P=0.001$)、NPI评分($P=0.001$)和CDR评分($P=0.006$)较高,MMSE评分($P=0.001$)和MoCA评分($P=0.000$)较低,其余各项资料组间差异无统计学意义(均$P>0.05$,表4)。

本组58例患者根据MMSE评分分为轻度痴呆组(评分为21~26,15例)、中度痴呆组(评分为10~20,23例)和重度痴呆组(评分为<10,20例)。3组患者高血压比例($P=0.005$)、Hcy($P=0.003$)、伴脑白质病变比例($P=0.017$)、Fazekas总评分($P=0.001$)、脑室旁白质高信号Fazekas评分($P=0.038$)和脑深部白质高信号Fazekas评分($P=0.000$)差异有统计学意义,进一步两两比较,重度痴呆组高血压比例($\chi^2=6.702$,$P=0.010$;Fisher确切概率法:$P=0.006$)、Hcy($P=0.039$,0.001)、Fazekas总评分($Z=2.898$,$P=0.004$;$Z=3.223$,$P=0.001$)、脑深部白质高信号Fazekas评分($Z=2.807$,$P=0.005$;$Z=4.144$,$P=0.000$)均高于中度痴呆组和轻度痴呆组,仅伴脑白质病变比例高于轻度痴呆组(Fisher确切概率法:$P=0.008$),脑室旁白质高信号Fazekas评分高于中度痴呆组($Z=2.567$,$P=0.010$),中度痴呆组脑深部白质高信号Fazekas评分亦高于轻度痴呆组($Z=2.950$,$P=0.003$);其余各项指标组间差异无统计学意义(均$P>0.05$,表5)。

本组58例患者根据是否合并高血压,分为阿尔茨海默病合并高血压组(合并高血压组,24例)和不合并高血压组(不合并高血压组,34例)。与不合并高血压组相比,合并高血压组患者Fazekas总评分($P=0.001$)和脑深部白质高信号Fazekas评分($P=0.000$)较高,而脑室旁白质高信号Fazekas评分组间差异无统计学意义($P=0.141$,表6)。

讨 论

阿尔茨海默病是一种神经元功能障碍性疾病,不仅累及神经元,同时也可累及白质导致脑白质病变[16]。脑白质病变作为阿尔茨海默病发生风险的早期预测因素,其严重程度可影响疾病进程[17-18]。2014年,来自荷兰和西班牙的两项研究显示,阿尔茨海默病患者脑白质病变发生率分别为79%和67.9%[19-20]。本研究结果显示,阿尔茨海默病患者脑白质病变患病率约为72.41%(42/58),与文献报道相近。

既往研究显示,高龄、高血压、糖尿病、高同型

表4 中至重度WML组与无或轻度WML组患者临床资料和神经心理学测验评分的比较

Table 4. Comparison of clinical data and neuropsychological scale in patients with different degrees of WML

观察指标	无或轻度WML组(n=32)	中至重度WML组(n=26)	统计量值	*P*值
性别[例(%)]			3.766	0.052
男性	18(56.25)	8(30.77)		
女性	14(43.75)	18(69.23)		
年龄($\bar{x}\pm s$,岁)	62.16±6.82	65.00±7.48	1.512	0.136
发病年龄($\bar{x}\pm s$,岁)	59.88±6.63	60.42±7.59	0.293	0.770
受教育程度($\bar{x}\pm s$,年)	10.97±3.66	10.19±3.09	0.861	0.393
BMI($\bar{x}\pm s$,kg/m^2)	22.86±3.40	23.18±4.03	0.328	0.744
高血压[例(%)]	7(21.88)	17(65.38)	11.195	0.001
冠心病[例(%)]	4(12.50)	6(23.08)	—	0.319
糖尿病[例(%)]	7(21.88)	8(30.77)	0.592	0.442
痴呆家族史[例(%)]	9(28.13)	9(34.62)	0.204	0.652
吸烟史[例(%)]	11(34.38)	8(30.77)	0.085	0.771
饮酒史[例(%)]	9(28.13)	6(23.08)	0.191	0.662
空腹血糖($\bar{x}\pm s$,mmol/L)	5.77±1.42	6.10±1.16	0.961	0.341
TC($\bar{x}\pm s$,mmol/L)	5.06±1.05	5.54 ±1.39	1.505	0.138
TG($\bar{x}\pm s$,mmol/L)	1.45±0.56	1.28±0.44	1.250	0.216
LDL-C($\bar{x}\pm s$,mmol/L)	3.18±0.73	3.73±0.88	2.573	0.013
HDL-C($\bar{x}\pm s$,mmol/L)	1.39±0.36	1.51±0.31	1.354	0.181
Hcy($\bar{x}\pm s$,μmol/L)	12.93±5.23	14.51±5.64	1.107	0.273
MMSE($\bar{x}\pm s$)	16.53±5.84	10.31±7.02	3.686	0.001
MoCA($\bar{x}\pm s$)	12.50±5.77	5.65±4.20	5.225	0.000
ADL[$M(P_{25},P_{75})$]	25.00 (22.25,31.75)	35.00 (28.00,52.00)	3.269	0.001
HAMD-21 [$M(P_{25},P_{75})$]	5.00 (3.25, 8.00)	6.00 (4.00,12.00)	1.116	0.264
NPI[$M(P_{25},P_{75})$]	5.50 (2.25,10.50)	13.00 (11.00,23.00)	3.439	0.001
CDR[$M(P_{25},P_{75})$]	1.00 (0.63, 2.00)	2.00 (1.00, 2.00)	2.740	0.006

— , Fisher's exact probability, Fisher 确切概率法。χ^2 test for comparison of sex, hypertension, diabetes, family history of dementia, smoking and drinking, Mann - Whitney *U* test for comparison of ADL, HAMD-21, NPI, CDR, and two-independent-sample *t* test for comparison of others,性别、高血压、糖尿病、痴呆家族史、吸烟史和饮酒史的比较行χ^2检验,ADL、HAMD-21、NPI和CDR评分的比较行Mann-Whitney *U*检验,其余各项指标的比较行两独立样本的*t*检验。WML, white matter lesion,脑白质病变;BMI, body mass index,体重指数;TC, total cholesterol,总胆固醇;TG, triglyceride,甘油三酯;LDL-C, low-density lipoprotein cholesterol,低密度脂蛋白胆固醇;HDL-C, high-density lipoprotein cholesterol,高密度脂蛋白胆固醇;Hcy, homocysteine,同型半胱氨酸;MMSE, Mini-Mental State Examination,简易智能状态检查量表;MoCA, Montreal Cognitive Assessment,蒙特利尔认知评价量表;ADL, Activities of Daily Living Scale,日常生活活动能力量表;HAMD-21, Hamilton Depression Rating Scale 21-Items,汉密尔顿抑郁量表21项;NPI, Neuropsychiatric Inventory,神经精神科问卷;CDR, Clinical Dementia Rating Scale,临床痴呆评价量表

半胱氨酸血症是脑白质病变的危险因素[21-22]。长期慢性高血压一方面可引发颅内小动脉壁玻璃样变性,管壁增厚,管腔狭窄,脑白质供血区血流量下降,导致脑白质病变;另一方面可导致血-脑屏障破坏,血管通透性增加,星形胶质细胞激活,大量炎性因子释放,进一步加重脑白质病变[23]。校正性别、年龄、高血压、吸烟史等危险因素后,阿尔茨海默病患者血浆Hcy水平每升高5 μmol/L,脑白质病变相对风险增加1.4倍[24]。在本研究中,WML组高血压比例高于无WML组,且中至重度WML组高血压比例高于无或轻度WML组,而在合并高血压的阿尔茨海默病患者中脑白质病变程度更严重,尤以脑深部白质高信号显著。Hcy是动脉粥样硬化的危险因素,且与认知功能障碍相关[25]。本研究不同脑白质病变严重程度组Hcy水平差异无统计学意义,但重度痴呆组Hcy水平高于中度和轻度痴呆组。

脑白质病变与认知功能减退密切相关,具体机制尚不明确。脑白质病变的潜在病理表现为脑小血管病变致慢性缺血,进而产生脱髓鞘改变和轴突缺失,可能通过皮质和皮质下结构间联系纤维的丢失、减缓神经传导速度或损伤传导束完整性,最终导致认知功能减退[26-27]。另有研究发现,脑白质病变可通过激活丝裂原激活蛋白激酶(MAPK)促进tau蛋白磷酸化,加速神经原纤维缠结(NFTs)形成。从机制上推测,脑白质病变和阿尔茨海默病的β-淀粉样蛋白(Aβ)沉积增加可能存在共同的病变途径,如神经炎症、显微结构改变或皮质萎缩,最终中断关键的脑网络,显著降低认知储备[28]。本研究结果显示,与无WML组相比,WML组患者认知功能(MMSE和MoCA评分)下降,进一步分析各认知域发现,注意力和计算力、命名、复述、回忆能力等认知域均明显受损。2018年的Meta分析显示,普通人群脑白质病变程度与视空间执行功能、处理速度、记忆力和语言功能呈负相关[29]。同年,另一项旨在量化轻度认知损害(MCI)和阿尔茨海默病患者脑白质高信号与特定认知域关联的Meta分析显示,脑白质高信号体积与记忆力、执行功能、注意力和处理速度下降显著相关[30]。LADIS(Leukokraurosis and Disability)研究显示,对于非痴呆人群,脑白质病变与认知功能障碍相关,其认知功能障碍随着脑白质病变程度的加重而逐渐加重[31],与本研究结果基本一致。

脑白质病变对认知功能的影响不仅与脑白质

表5 不同痴呆程度患者临床资料和神经心理学测验评分的比较

Table 5. Comparison of scores of clinical data and neuropsychological scale in patients with different degrees of AD

观察指标	轻度痴呆组（n=15）	中度痴呆组（n=23）	重度痴呆组（n=20）	统计量值	*P*值
性别(例)				2.194	0.334
男性	9/15	10/23	7/20		
女性	6/15	13/23	13/20		
年龄($\bar{x}\pm s$,岁)	62.93±8.88	62.87±6.46	64.45±6.89	0.298	0.743
发病年龄($\bar{x}\pm s$,岁)	60.67±8.89	60.09±6.02	59.75±6.87	0.071	0.931
受教育程度($\bar{x}\pm s$,年)	11.93±3.45	10.48±3.68	9.80±2.88	1.759	0.182
BMI($\bar{x}\pm s$,kg/m^2)	24.17±4.18	22.39±2.76	22.83±4.14	1.106	0.338
高血压(例)	3/15	7/23	14/20	10.716	0.005
冠心病(例)	2/15	5/23	3/20	0.563	0.826
糖尿病(例)	7/15	3/23	5/20	5.365	0.068
痴呆家族史(例)	6/15	6/23	6/20	0.813	0.666
吸烟史(例)	4/15	9/23	6/20	0.746	0.689
饮酒史(例)	5/15	5/23	5/20	0.648	0.723
空腹血糖($\bar{x}\pm s$,mmol/L)	6.46±1.78	5.59±0.97	5.87±1.17	2.090	0.134
TC($\bar{x}\pm s$,mmol/L)	4.93±1.15	5.44±1.44	5.34±0.98	0.809	0.451
TG($\bar{x}\pm s$,mmol/L)	1.36±0.44	1.35±0.55	1.41±0.53	0.064	0.938
LDL-C($\bar{x}\pm s$,mmol/L)	3.11±0.76	3.53±0.86	3.54±0.83	1.463	0.241
HDL-C($\bar{x}\pm s$,mmol/L)	1.29±0.34	1.53±0.36	1.46±0.29	2.568	0.086
Hcy($\bar{x}\pm s$,μmol/L)	10.48±3.73	13.23±4.47	16.46±6.21	6.291	0.003
伴WML(例)	7/15	17/23	18/20	8.100	0.017
Fazekas总评分[$M(P_{25},P_{75})$]	0.00 (0.00,3.00)	2.00 (0.00,3.00)	3.00 (2.25,4.75)	13.658	0.001
PWMH Fazekas评分[$M(P_{25},P_{75})$]	0.00 (0.00,2.00)	1.00 (0.00,1.00)	2.00 (1.00,2.00)	6.540	0.038
DWMH Fazekas评分[$M(P_{25},P_{75})$]	0.00 (0.00,1.00)	1.00 (0.00,1.00)	2.00 (1.00,2.00)	21.550	0.000

—，Fisher's exact probability，Fisher确切概率法。χ^2 test for comparison of sex, hypertension, coronary heart disease, diabetes, family history of dementia, smoking, drinking and WML, Mann-Whitney *U* test for comparison of total Fazekas, PWMH Fazekas and DWMH Fazekas scores, and two-independent-sample *t* test for comparison of others，性别、高血压、冠心病、糖尿病、痴呆家族史、吸烟史、饮酒史和伴WML的比较行χ^2检验，Fazekas总评分、PWMH Fazekas评分和DWMH Fazekas评分的比较行Mann-Whitney *U*检验，其余各项指标的比较行两独立样本的*t*检验。BMI, body mass index，体重指数；TC, total cholesterol，总胆固醇；TG, triglyceride，甘油三酯；LDL-C, low-density lipoprotein cholesterol，低密度脂蛋白胆固醇；HDL-C, high-density lipoprotein cholesterol，高密度脂蛋白胆固醇；Hcy, homocysteine，同型半胱氨酸；WML, white matter lesion，脑白质病变；PWMH, periventricular white matter hyperintensities，脑室旁白质高信号；DWMH, deep white matter hyperintensities，脑深部白质高信号

表6 合并高血压组与不合并高血压组患者Fazekas评分的比较[$M(P_{25},P_{75})$]

Table 6. Influence of hypertension history on total Fazekas scores, PWMH and DWMH Fazekas scores of AD patients [M (P_{25}, P_{75})]

观察指标	不合并高血压组（n=34）	合并高血压组（n=24）	*Z*值	*P*值
Fazekas总评分	2.00(0.00,3.00)	3.00(2.00,4.75)	3.284	0.001
PWMH Fazekas评分	1.00(0.00,2.00)	1.00(0.25,2.00)	1.473	0.141
DWMH Fazekas评分	1.00(0.00,1.00)	2.00(1.00,2.75)	4.083	0.000

PWMH, periventricular white matter hyperintensities，脑室旁白质高信号；DWMH, deep white matter hyperintensities，脑深部白质高信号

病变程度有关，还与脑白质病变部位相关。既往认为，脑室旁白质高信号与脑深部白质高信号的作用存在差异，且对认知功能的影响存在异质性，各项研究结果尚存争议。一项针对糖尿病的研究发现，脑室旁白质高信号与注意力和执行功能降低相关，脑深部白质高信号与信息处理速度减慢相关[32]。Soriano-Raya等[33]认为，与脑室旁白质高信号相比，脑深部白质高信号与视空间执行功能、视空间能力、语言流畅性、精神运动处理速度相关性更强。本研究根据痴呆程度分组发现，脑白质病变患病率、Fazekas总评分、脑室旁白质高信号Fazekas评分、脑深部白质高信号Fazekas评分在轻度、中度、重度痴呆患者中存在差异，且脑深部白质高信号Fazekas评分随阿尔茨海默病痴呆程度的加重而逐渐增加，提示阿尔茨海默病患者脑深部白质高信号与认知功能的关系更密切，推测与认知处理速度和注意力下降有关。但来自台湾地区的研究显示，阿尔茨海默病患者脑白质病变程度与痴呆程度密切相关，且随痴呆程度的加重而加重，其中脑室旁白质高信号Fazekas评分随痴呆程度的加重而增加，而脑深部白质高信号Fazekas评分无明显改变[34]。上述研究结果存在差异，考虑可能与所纳入研究对象、样本量不同有关。

多项研究显示，脑白质病变亦影响神经精神行为，脑白质病变可以增加抑郁障碍的风险，表明脑白质病变与老年抑郁症相关[35]；脑白质完整性破坏还与情感淡漠密切相关[36]。目前针对阿尔茨海默病患者精神症状与脑白质病变的研究均认为血管因素参与其中，2016年Fischer等[37]发现，血管性危险因素与阿尔茨海默病精神症状的发生相关。Palmqvist等[38]认为，基底节区腔隙性梗死灶的血管病理改变可以增加妄想症的风险。本研究结果显示，WML组患者NPI评分高于无WML组，其中以妄想、抑郁/心境恶劣、情感淡漠/漠不关心发生率较高，且随着脑白质病变的进展，神经精神行为异常

加重。2017年的一项研究显示,阿尔茨海默病伴妄想的患者脑白质病变体积大于不伴妄想的患者[39]。同年,来自法国的一项针对痴呆人群的研究显示,抑郁情绪与脑深部白质高信号体积相关[40]。Hahn等[41]发现,阿尔茨海默病患者淡漠症状的发生与脑白质完整性破坏有关。Jonsson等[42]针对整体痴呆人群的研究结果与之相似,脑白质病变与情感淡漠相关,其内在机制可能是由于脑白质病变导致额叶至基底节和扣带回的神经网络联系破坏。脑白质病变亦与幻觉有关[43]。本研究结果显示,WML组幻觉发生率与无WML组无明显差异,与Lee等[44]的研究结果基本相符。既往研究显示,较大的脑白质病变体积与焦虑、运动行为异常、夜间干扰等症状有关[3],而本研究并未发现阿尔茨海默病伴脑白质病变患者焦虑、运动行为异常、夜间行为等症状与单纯阿尔茨海默病患者之间存在明显差异,可能与本研究样本量较小且并未对脑白质病变进行定量分析有关。

综上所述,脑白质病变在阿尔茨海默病患者中有较高的患病率,其对认知功能和神经精神行为的影响应引起临床医师更多的重视。脑白质病变可能是阿尔茨海默病预防与治疗的潜在靶点,修复受损的脑白质可能成为阿尔茨海默病治疗研究方向之一。因此,应重视早期脑白质病变危险因素的筛查和预防,发现有效治疗目标。本研究的局限性是,未对阿尔茨海默病*ApoE*基因型进行分类统计,未能阐明*ApoE*基因型是否对阿尔茨海默病患者脑白质病变产生影响。未来期待进一步扩大样本量,通过定量和更为精准的测量方法,以及分析阿尔茨海默病*ApoE*基因型,以进一步揭示脑白质病变对阿尔茨海默病的影响。

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