

老年血管性痴呆患者血清 ANGPTL4 和 sTLT-1 水平表达与其认知功能及预后的相关性研究

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摘要: **目的** 探讨老年血管性痴呆 (vascular dementia, VD) 患者血清血管生成素样蛋白 4 (angiopoietin-like protein 4, ANGPTL4)、可溶性骨髓细胞样转录因子-1 (soluble bone marrow cell-like transcription factor-1, sTLT-1) 水平表达与其认知功能和预后的相关性研究。**方法** 选取 2020 年 6 月~2022 年 6 月在河北燕达医院收治的 92 例老年血管性痴呆患者作为研究组, 根据简易精神状态量表 (minimum mental state examination, MMSE) 评分分为轻度组 ($n=30$)、中度组 ($n=36$) 和重度组 ($n=26$), 另选取同期健康体检者 92 例作为对照组。根据患者预后认知功能障碍情况分为 I~II 级和 III 级; 采用 ELISA 方法检测各组血清 ANGPTL4 和 sTLT-1 水平, 采用 Pearson 和 Spearman 法分析血清 ANGPTL4, sTLT-1 与 MOCA 评分的相关性; 采用 Logistic 回归分析老年血管性痴呆患者预后分级为 III 级的影响因素; 绘制受试者工作特征 (receiver operating characteristic, ROC) 曲线分析血清 ANGPTL4 和 sTLT-1 水平对老年血管性痴呆患者预后分级为 III 级的预测价值。**结果** 研究组血清 ANGPTL4 (987.57 ± 53.25 pg/ml) 水平显著低于对照组 (1108.35 ± 62.13 pg/ml), 血清 sTLT-1 (68.01 ± 5.15 pg/ml) 水平显著高于对照组 (50.12 ± 4.57 pg/ml), 差异具有统计学意义 ($t=14.158, 24.922$, 均 $P < 0.05$)。轻度、中度和重度组血清 ANGPTL4 水平和 MOCA 评分依次降低 ($F=33.495, 66.617$), 血清 sTLT-1 水平依次升高 ($F=66.718$), 差异具有统计学意义 (均 $P < 0.05$)。Pearson 法分析显示, 血清 ANGPTL4 与 sTLT-1 呈负相关 ($r=-0.621, P < 0.05$), Spearman 法分析显示, 血清 ANGPTL4 与 MoCA 评分呈正相关 ($r=0.545, P < 0.05$), sTLT-1 水平与 MoCA 评分呈负相关 ($r=-0.557, P < 0.05$)。III 级预后患者血清 ANGPTL4 (953.45 ± 51.16 pg/ml) 水平显著低于 I~II 级 (1005.76 ± 54.27 pg/ml), 血清 sTLT-1 (73.14 ± 5.40 pg/ml) 水平显著高于 I~II 级 (65.28 ± 5.02 pg/ml), 差异具有统计学意义 ($t=4.490, 6.967$, 均 $P < 0.05$)。Logistic 回归分析得知, ANGPTL4 低表达 [OR (95%CI): 5.089 (1.833 ~ 14.129)], sTLT-1 高表达 [OR (95%CI): 4.258 (1.739 ~ 10.428)] 均为影响老年血管性痴呆患者预后分级为 III 级的危险因素 ($P < 0.05$)。根据 ROC 曲线得知, 二者联合预测老年血管性痴呆患者预后分级为 III 级优于 ANGPTL4 和 sTLT-1 各自单独预测 ($Z=2.135, 3.268$, 均 $P < 0.05$)。**结论** 老年血管性痴呆患者血清 ANGPTL4 水平显著降低, sTLT-1 水平显著升高, ANGPTL4 和 sTLT-1 与认知功能和预后密切相关。

关键词: 血管性痴呆; 血管生成素样蛋白 4; 可溶性骨髓细胞样转录因子-1; 认知功能

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Correlation between Serum Levels of ANGPTL4 and sTLT-1 and Cognitive Function and Prognosis in Elderly Patients with Vascular Dementia

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Abstract: Objective To investigate the correlation between serum Angiopoietin-like protein 4 (ANGPTL4) and soluble bone marrow cell-like transcription factor-1 (sTLT-1) levels and cognitive function and prognosis in elderly patients with vascular dementia (VD). **Methods** A total of 92 elderly patients with vascular dementia admitted to Hebei Yanda Hospital from June 2020 to June 2022 were selected as the study group. They were divided into mild ($n=30$), moderate ($n=36$) and severe groups ($n=26$) according to the minimum mental state examination (MMSE) score, and 92 patients with healthy physical examination during the same period were selected as the control group. According to the prognosis of patients, the cognitive dysfunction was divided into grade I~II and grade III. ELISA method was used to detect the levels of serum ANGPTL4 and sTLT-1. Pearson and Spearman methods were used to analyze the correlation between serum ANGPTL4 and sTLT-1 and MOCA scores. Logistic regression analysis was used to analyze the influencing factors of the prognostic grade III of elderly patients with vascular dementia. The receiver operating characteristic (ROC) curve was plotted to analyze the predictive value of serum ANGPTL4 and

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sTLT-1 levels in the prognostic grade III in elderly patients with vascular dementia. **Results** The serum ANGPTL4 level (987.57 ± 53.25 pg/ml) in the study group was lower than that in the control group ($1\ 108.35 \pm 62.13$ pg/ml), and the serum sTLT-1 (68.01 ± 5.15 pg/ml) level was higher than that in the control group (50.12 ± 4.57 pg/ml), with significant differences ($t=14.158, 24.922$, all $P<0.05$). Serum ANGPTL4 levels and MOCA scores were decreased sequentially in the mild, moderate and severe groups ($F=33.495, 66.617$), while serum sTLT-1 level was increased sequentially ($F=66.718$), and the differences were statistically significant (all $P<0.05$), respective. Pearson analysis showed that serum ANGPTL4 was negatively correlated with sTLT-1 ($r=-0.621, P<0.05$). Spearman analysis showed serum levels of ANGPTL4 and sTLT-1 were positively and negatively correlated with MoCA scores, respectively ($r=0.545, -0.557$, all $P<0.05$). The serum ANGPTL4 level (953.45 ± 51.16 pg/ml) in the prognostic patients of grade III was lower than that of grade I ~ II ($1\ 005.76 \pm 54.27$ pg/ml), and the serum level of sTLT-1 (73.14 ± 5.40 pg/ml) was higher than that of grade I~II (65.28 ± 5.02 pg/ml), with significant differences ($t=4.490, 6.967$, all $P<0.05$). Logistic regression analysis showed low expression of ANGPTL4 [OR(95%CI): 5.089 (1.833~14.129)] and high expression of sTLT-1 [OR(95%CI): 4.258 (1.739~10.428)] were risk factors affecting the prognosis of elderly patients with vascular dementia ($P<0.05$). According to the ROC curve, the combined prediction of two for the grade III prognosis of elderly vascular dementia patients was better than the individual prediction of ANGPTL4 and sTLT-1 ($Z=2.135, 3.268$, all $P<0.05$). **Conclusion** Serum ANGPTL4 level was decreased but sTLT-1 level was increased in elderly patients with vascular dementia, and ANGPTL4 and sTLT-1 were closely related to cognitive function and prognosis.

Keywords: vascular dementia; angiotensin-like protein 4; soluble bone marrow cell-like transcription factor-1; cognitive function

血管性痴呆 (vascular dementia, VD) 是由脑血管疾病引起的认知功能障碍综合征, 也是中枢神经系统退行性疾病, 由缺血性脑卒中以及慢性脑供血不足导致, 临床症状为认知功能减退、社会功能下降^[1], 患者病情呈现波动性或者阶梯样加重, 严重影响患者的生活质量^[2]。血管性痴呆患者在发病早期治疗可避免病情恶化, 还可改善患者预后^[3]。因此, 在临床寻找与患者认知功能和预后相关的诊断标志物对治疗和改善患者预后尤为重要。血管性痴呆发病机制复杂, 有研究证实其发生发展与颈动脉粥样硬化有关^[4], 血管生成素样蛋白4 (angiotensin like protein 4, ANGPTL4) 是新发现的一种与人类有关的血管生成素样蛋白, 可稳定动脉粥样硬化斑块并抑制其发展^[5]。血清 ANGPTL4 参与颈动脉粥样硬化斑块稳定性的生物学发展^[6]。可溶性骨髓细胞样转录因子-1 (soluble bone marrow cell-like transcription factor-1, sTLT-1) 是血小板活化后由髓样细胞触发受体样转录因子-1 裂解产生的可溶性片段, 有研究证实其与动脉粥样硬化有关, 会促进动脉粥样硬化的进展^[7]。基于此, 猜测 ANGPTL4 与 sTLT-1 可能与血管性痴呆的生物学发展有关, 且目前关于 ANGPTL4, sTLT-1 与血管性痴呆的研究鲜有报道, 因此, 本研究主要探讨血管性痴呆患者血清 ANGPTL4 和 sTLT-1 表达水平, 分析其与认知功能和预后的关系, 旨在为临床中老年血管性痴呆患者的诊疗和预后提供研究方向。

1 材料与方法

1.1 研究对象 选取2020年6月~2022年6月河北燕达医院收治的老年血管性痴呆患者92例作为

研究组, 根据简易精神状态量表 (minimum Mental State Examination, MMSE) 评分将患者分为轻度组 (> 20 分, $n=30$)、中度组 ($10\sim20$ 分, $n=36$) 和重度组 (< 10 分, $n=26$)。纳入标准: ①所选患者符合《神经病学》中关于老年血管性痴呆诊断标准^[8], 患者表现为认知功能障碍, 记忆力低下; ②经过临床和影像学检查有局灶性神经系统症状, 脑室周围有白质损伤; ③患者病情稳定; ④临床资料完整; ⑤患者文化程度在中学以上。排除标准: ①并发心脏、肝脏以及肺脏等功能障碍者; ②因其他脑血管原因引起的认知功能障碍; ③并发恶性肿瘤; ④并发免疫系统疾病者。研究组男性57例, 女性35例, 年龄 71.35 ± 5.76 岁, 体质指数 (BMI) 23.41 ± 2.62 kg/m², 病程 4.67 ± 1.02 年; 有吸烟史54例, 饮酒史38例; 另选取同期健康体检者92例作为对照组, 男性59例, 女性33例, 年龄 72.04 ± 6.01 岁, BMI 23.53 ± 2.64 kg/m², 有吸烟史50例, 饮酒史35例。两组一般资料比较差异无统计学意义 ($\chi^2/t=0.093, 0.795, 0.309, 0.354, 0.204$, 均 $P>0.05$)。患者或家属签署承诺书。本院伦理委员会批准本研究 (批号 2022051132)。

1.2 仪器与试剂 血清 ANGPTL4 的 ELISA 试剂盒 (武汉菲恩公司, 货号 FN-EH0038), sTLT-1 的酶联免疫吸附 (enzyme-linked immunosorbent assay, ELISA) 试剂盒 (武汉菲恩公司, 货号 FN-EH0706), 全自动酶标仪 (武汉中美公司, 型号 KHB ST-360)

1.3 方法

1.3.1 血清 ANGPTL4, sTLT-1 水平的检测: 采集对照组体检时静脉血 (空腹) 5 ml, 采集研究组

入组当天静脉血（空腹）5 ml，3 000r/min 离心 10 min，离心半径 10 cm，吸取上清液采用 ELISA 法检测血清 ANGPTL4，sTLT-1 水平，操作按照说明书进行。

1.3.2 认知功能评估：认知功能采用蒙特利尔认知评估（Montreal cognitive assessment，MoCA）量表进行评估，主要包括执行功能、语言、记忆、注意与集中、抽象思维等 8 个领域 11 个项目，总分为 30 分，得分越高说明认知功能越好。

1.3.3 预后：研究组患者出院后对其进行 6 个月随访，根据日常生活活动能力量表（activities of daily living，ADL）评价患者预后情况，ADL 评分总共包括 11 个评分项目，总分为 100 分，得分越高说明预后越好，ADL 评分 ≤ 40 分为重度（III 级）预后功能障碍，41 ~ 60 分为中度（II 级）预后功能障碍，61 ~ 99 分为轻度（I 级）预后功能障碍。

1.4 统计学分析 SPSS 25.0 软件分析数据。符合正态分布的计量资料以均数 ± 标准差 ($\bar{x} \pm s$) 表示，行独立样本 *t* 检验。多组间比较为单因素方差分析。

表 1 不同严重程度患者血清 ANGPTL4，sTLT-1 水平和 MoCA 评分的比较 ($\bar{x} \pm s$)

项 目	轻度组 (n=30)	中度组 (n=36)	重度组 (n=26)	F 值	P 值
ANGPTL4 (pg/ml)	1 041.67 ± 54.93	987.78 ± 52.78 ^a	924.86 ± 51.96 ^{ab}	33.495	< 0.001
sTLT-1 (pg/ml)	59.54 ± 4.65	70.01 ± 4.93 ^a	75.02 ± 6.02 ^{ab}	66.718	< 0.001
MoCA (分)	23.35 ± 3.60	18.59 ± 3.32 ^a	13.59 ± 2.24 ^{ab}	66.617	< 0.001

注：^a与轻度组相比，*q*=5.788，11.575，11.574；15.787，8.625，16.317，均 *P* < 0.05；^b与中度组相比，*q*=6.491，5.319，8.703，均 *P* < 0.05。

2.3 老年血管性痴呆患者血清 ANGPTL4，sTLT-1 与 MOCA 评分的相关性 Pearson 法分析显示，血清 ANGPTL4 与 sTLT-1 呈负相关 (*r*=-0.621，*P* < 0.001)；Spearman 法分析显示，血清 ANGPTL4 和 sTLT-1 分别与 MoCA 评分呈正、负相关 (*r*=0.545，-0.557，均 *P* < 0.001)。

2.4 不同预后老年血管性痴呆患者血清 ANGPTL4，sTLT-1 水平的比较 与 I~II 级相比，III 级预后患者血清 ANGPTL4 水平显著降低 (953.45 ± 51.16pg/ml vs 1 005.75 ± 54.27pg/ml)，血清 sTLT-1 水平

表 2 影响老年血管性痴呆患者预后 III 级的 Logistic 回归分析结果

因 素	β	SE	Waldχ ²	P	OR	95%CI
ANGPTL4	1.627	0.521	9.753	0.002	5.089	1.833~14.129
sTLT-1	1.449	0.457	10.050	0.002	4.258	1.739~10.428

2.6 血清 ANGPTL4，sTLT-1 水平对老年血管性痴呆患者预后分级为 III 级的预测价值 见图 1，表 3。根据 ROC 曲线得知，血清 ANGPTL4 预测老年血管性痴呆患者预后分级为 III 级的 AUC 为 0.869，血清 sTLT-1 预测老年血管性痴呆患者预后分级为 III 级的 AUC 为 0.820，二者联合预测老年血管性痴呆患者预后分级为 III 级的 AUC 为 0.906，二者联合优于各自单独预测，差异具有统计学意义

进一步两两比较采用 SIVK-*q* 检验。计数资料以例 (*n*) 表示，行 χ^2 检验。采用 Pearson 和 Spearman 法分析血清 ANGPTL4，sTLT-1 与 MoCA 评分的相关性；采用 Logistic 回归分析老年血管性痴呆患者预后分级为 III 级的影响因素；ROC 曲线来分析血清 ANGPTL4，sTLT-1 水平对老年血管性痴呆患者预后分级为 III 级的预测价值。*P* < 0.05 为差异有统计学意义。

2 结果

2.1 研究组和对照组血清 ANGPTL4，sTLT-1 水平的比较 与对照组相比，研究组血清 ANGPTL4 水平降低 (987.57 ± 53.25 pg/ml vs 1 108.35 ± 62.13 pg/ml)，血清 sTLT-1 水平升高 (68.01 ± 5.15 pg/ml vs 50.12 ± 4.57 pg/ml)，差异具有统计学意义 (*t*=14.158，24.922，均 *P* < 0.05)。

2.2 不同严重程度患者血清 ANGPTL4，sTLT-1 水平和 MoCA 评分的比较 见表 1。轻度、中度和重度组血清 ANGPTL4 和 MoCA 评分依次降低，血清 sTLT-1 水平依次升高，差异具有统计学意义 (均 *P* < 0.05)。

显著高升高 (73.14 ± 5.40 pg/ml vs 65.28 ± 5.02pg/ml)，差异具有统计学意义 (*t*=4.490，6.967，均 *P* < 0.05)。

2.5 Logistic 回归分析老年血管性痴呆患者预后 III 级的影响因素 见表 2。以老年血管性痴呆患者预后分级是否为 III 级作为因变量 (III 级 =1，I~II 级 =0)，以 ANGPTL4，sTLT-1 为自变量 (均为实测值)，Logistic 回归分析得知，ANGPTL4 低表达，sTLT-1 高表达均为影响老年血管性痴呆患者预后分级为 III 级的危险因素 (*P* < 0.05)。

(*Z*=2.135，3.268，均 *P* < 0.05)。

3 讨论

近年来脑血管疾病发病率不断升高，致使血管性痴呆发病率也呈上升趋势，血管性痴呆患者在临床表现为语言、记忆等多个功能发生障碍，大多由血管疾病引起，严重影响患者健康^[9-10]。关于血管性痴呆的发病机制有学者认为其与高血压、糖尿病以及动脉粥样硬化等有关，而且动脉粥样硬化是导

致血管性痴呆的关键因素^[4]。有效评估血管性痴呆患者痴呆程度,尽可能早期发现并进行干预可延缓患者病情进展,从而改善患者预后^[11]。

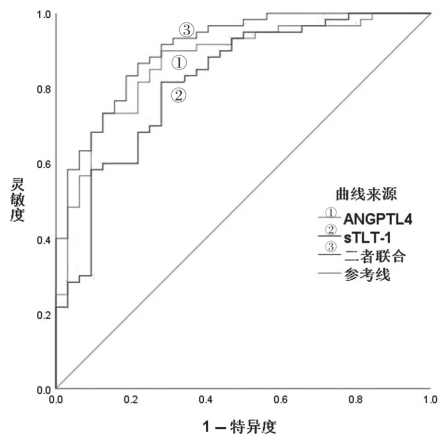


图1 血清 ANGPTL4, sTLT-1 水平对老年血管性痴呆患者预后分级为 III 级的预测价值

表3 血清 ANGPTL4, sTLT-1 水平预测老年血管性痴呆患者预后分级为 III 级的价值

项目	AUC	95%CI	敏感度(%)	特异度(%)	截断值
ANGPTL4	0.869	0.793~0.945	72.03	87.52	971.254 pg/ml
sTLT-1	0.820	0.729~0.912	78.43	81.38	69.724 pg/ml
联合预测	0.906	0.844~0.967	85.75	77.31	-

ANGPTL4 是一种分泌型蛋白,其与机体血管生成、脂代谢以及糖代谢等多个生物学过程密切相关,还在多种脑血管疾病中发挥重要作用^[12]。ANGPTL4 可以抑制脂蛋白脂肪酶的活性,从而水解循环中的脂质蛋白来促进机体吸收脂质,其还能将活性脂蛋白脂肪酶的片段转化为无活性单体,从而不可逆的抑制脂蛋白脂肪酶,使机体脂质吸收和泡沫细胞形成减少,减缓动脉粥样硬化发展^[13-14]。ANGPTL4 降低会抑制巨噬细胞吸收脂肪酸,增加吸收脂质,加快动脉粥样硬化发展^[15]。有研究发现 ANGPTL4 在老年冠心病患者血清中异常降低,参与冠脉病变的进展过程^[16]。ANGPTL4 能稳定动脉粥样硬化斑块,并通过 KLF4 下调来调节血管平滑肌细胞的表型转变^[17]。本研究发现,血清 ANGPTL4 水平随着病情严重程度降低,与夏瑞雪等^[6]研究相似,说明 ANGPTL4 与患者疾病严重程度有关,其可能参与血管性痴呆的发生发展。

sTLT-1 是一种当血小板表面 TLT-1 发生裂解后产生的可溶性蛋白,其可以促进肌动蛋白聚合,在内皮细胞上黏附血小板,从而促进动脉粥样硬化^[18]。当 sTLT-1 进入外周血液时,会促进血小板聚集,并且与内皮细胞黏附,参与早期血管内皮结构和功能损伤,导致出现血管栓塞或动脉粥样硬化^[19],血

清 sTLT-1 在冠状动脉疾病中显著升高,可能是与冠状动脉有关的新标志物^[20]。有研究发现 sTLT-1 在急性脑梗死患者血清中显著升高,还与神经功能有关^[21]。另有研究发现在缺血性脑卒中患者血清中 sTLT-1 异常升高会加剧机体内皮损伤^[22]。本研究发现血清 sTLT-1 水平随着病情严重程度升高,与 FU 等^[23]研究相似,说明 sTLT-1 可能参与血管性痴呆的生物学发展,而且推测在机体发生脑血管疾病后, sTLT-1 异常升高会诱导血小板活化,加速动脉粥样硬化斑块形成,从而导致病情加重。

此外,血清 ANGPTL4 与 sTLT-1 水平呈负相关,说明二者可能共同参与调节血管性痴呆,后续对其具体调控机制进一步研究。血清 ANGPTL4 与 MoCA 评分呈正相关,血清 sTLT-1 和 MoCA 评分呈负相关,说明血清 ANGPTL4 和 sTLT-1 与认知功能有关。进一步研究发现,III 级预后患者血清 ANGPTL4 水平显著低于 I~II 级, sTLT-1 水平显著高于 I~II 级, ANGPTL4, sTLT-1 是影响老年血管性痴呆患者预后分级为 III 级的危险因素,说明 ANGPTL4 和 sTLT-1 与患者预后密切相关。有研究发现血清联合检测可以预测血管性痴呆患者预后功能障碍,优于各自单独预测,联合预测可为血管性痴呆患者预后提供参考,提高预测价值^[24]。本研究根据 ROC 曲线得知, ANGPTL4 和 sTLT-1 二者联合预测老年血管性痴呆患者预后分级为 III 级优于各自单独预测,说明二者联合可以更好地预测患者预后,从而可以优先开展相关治疗并改善患者的预后。本研究尚存在局限性,如未研究 ANGPTL4 和 sTLT-1 对血管性痴呆的具体调控机制,样本量不足等,后续将会扩大样本量对本研究进行验证。

综上所述,老年血管性痴呆患者血清 ANGPTL4 水平显著降低, sTLT-1 水平显著升高,二者与患者认知功能和预后密切相关。

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