·临床研究·

老年2型糖尿病患者认知功能障碍影响因素分析

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【摘 要】 目的 探讨老年2型糖尿病(T2DM)患者认知功能障碍发生的影响因素。**方法** 回顾性分析2017年6月至2018年5月首都医科大学宣武医院内分泌科2型糖尿病患者204例,根据简易版蒙特利尔认知评估(MoCA)量表结果分为认知功能障碍组98例和认知功能正常组106例。记录2组患者实验室检查结果,慢性肾脏病流行病学合作研究(CKD-EPI)公式计算估算肾小球滤过率(eGFR)。采用SPSS 19.0统计软件对数据进行分析。组间比较采用t检验、Mann-Whitney U检验或χ^2检验。多因素logistic回归分析认知功能障碍的危险因素。**结果** 认知功能障碍组相比认知功能正常组患者年龄[(68.4±7.7) *vs* (66.0±6.7)岁]、骨质疏松[35.71%(35/98) *vs* 19.81%(21/106)]和eGFR<60 ml/(min·1.73 m^2)比例[26.53%(26/98) *vs* 12.26%(13/106)]高,MoCA分值[(20.36±4.07) *vs* (27.02±1.49)分]和受教育时间[(8.85±4.14) *vs* (12.35±3.30)年]低,差异均具有统计学意义($P<0.05$)。多因素logistic回归分析结果表明年龄($OR=1.05$, 95%CI 1.01~1.10;$P=0.011$)和eGFR<60 ml/(min·1.73 m^2)[$OR=2.15$, 95%CI 1.08~4.26;$P=0.029$]为老年2型糖尿病患者认知功能障碍的独立危险因素。**结论** 年龄和eGFR<60 ml/(min·1.73 m^2)是老年2型糖尿病患者认知功能障碍的危险因素,控制患者血糖同时要监测患者肾功能,预防认知功能障碍的发生和进展。

【关键词】 糖尿病,2型;认知功能障碍;肾功能不全
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Influencing factors associated with cognitive dysfunction in the elderly with type 2 diabetes mellitus

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【Abstract】 Objective To explore the influencing factors associated with cognitive dysfunction in the elderly with type 2 diabetes mellitus (T2DM). **Methods** A total of 204 hospitalized T2DM old patients (≥60 years old) admitted in our department from June 2017 to May 2018 were enrolled in the study. According to the result of Montreal Cognitive Assessment (MoCA) test, they were divided into the cognitive dysfunction group ($n=98$) and normal cognitive function group ($n=106$). The indicators of physical examination and laboratory tests were collected. The estimated glomerular filtration rate (eGFR) was calculated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. SPSS statistics 19.0 was used for data analysis, and Chi-square test, Student's t test or Mann-Whitney U test was employed for comparison between the groups. Multivariate logistic regression analysis was used to assess the risk factors for cognitive dysfunction. **Results** The cognitive dysfunction group was older in age [(68.4±7.7) *vs* (66.0±6.7) years], and had significantly higher proportions of the patients with osteoporosis [35.71%(35/98) *vs* 19.81%(21/106)] and eGFR <60 ml/(min·1.73 m^2) [26.53%(26/98) *vs* 12.26%(13/106)], but lower MoCA score [(20.36±4.07) *vs* (27.02±1.49)] and shorter educational duration [(8.85±4.14) *vs* (12.35±3.30) years] when compared with the normal cognitive function group (all $P<0.05$). Multivariate logistic regression analysis showed that age ($OR=1.05$, 95%CI 1.01-1.10; $P=0.011$) and eGFR <60 ml/(min·1.73 m^2) ($OR=2.15$, 95%CI 1.08-4.26; $P=0.029$) were independent risk factors for cognitive dysfunction. **Conclusions** Age and eGFR <60 ml/(min·1.73 m^2) are risk factors for cognitive dysfunction in the elderly with T2DM. So, controlling blood glucose and monitoring renal function are helpful to prevent the occurrence and progress of cognitive dysfunction.

【Key words】 diabetes mellitus, type 2; cognitive dysfunction; renal dysfunction

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随着糖尿病患病率不断增高,与其相关的并发症对个人和社会造成了沉重的负担,其中糖尿病肾脏疾病的发病率达 25%~40%,已成为终末期肾病的主要病因[1]。研究表明慢性肾脏病(chronic kidney disease,CKD)是认知功能障碍和痴呆的危险因素[2,3]。一项关于社区老年人研究结果表明 CKD 患者估算肾小球滤过率(estimated glomerular filtration rate, eGFR)<60 ml/(min · 1.73 m^2)与认知功能障碍风险增加显著相关[4]。而糖尿病患者较无糖尿病患者更易出现认知功能障碍,痴呆风险显著增高[5]。目前治疗痴呆的药物并不多,因此确定影响糖尿病患者认知功能障碍的因素很重要。本研究的目的是探索老年 2 型糖尿病患者认知功能障碍的影响因素,以期为早期预防提供理论依据。

1 对象与方法

1.1 研究对象

回顾性分析 2017 年 6 月至 2018 年 5 月首都医科大学宣武医院内分泌科 2 型糖尿病患者 204 例,根据简易版蒙特利尔认知评估(Montreal Cognitive Assessment,MoCA)量表结果分为认知功能障碍组 98 例和认知功能正常组 106 例。纳入标准:年龄≥60 岁;符合 1999 年世界卫生组织糖尿病诊断标准中 2 型糖尿病诊断标准[6]。排除标准:严重感染和糖尿病急性并发症;患精神疾病、脑炎和帕金森病;甲状腺功能异常;酗酒、药物滥用者;急性脑血管病发病≤3 个月或听力言语障碍不能配合检查。所有患者均签署知情同意书。

1.2 方法

1.2.1 临床指标检测 测定患者身高和体质量,并计算体质量指数(body mass index,BMI)。禁食 8 h 后空腹抽肘静脉血测空腹血糖(fasting blood glucose,FBG)、糖化血红蛋白(glycosylated hemoglobin A1c,HbA1c)、空腹胰岛素、空腹 C 肽、甘油三酯(triglycerides,TG)、总胆固醇(total cholesterol,TC)、低密度脂蛋白胆固醇(low-density lipoprotein cholesterol,LDL-C)、高密度脂蛋白胆固醇(high-density lipoprotein cholesterol,HDL-C)、血肌酐(serum creatinine,SCr)、尿酸(uric acid,UA)、C 反应蛋白(C-reactive protein,CRP)和白细胞介素-6(interleukin-6,IL-6)水平。

慢性肾脏病流行病学合作研究公式(chronic kidney disease epidemiology collaboration,CKD-EPI)计算 eGFR 水平。eGFR<60 ml/(min · 1.73 m^2)判定为肾功能不全[3]。留取 2 次晨尿测尿白蛋白肌酐比(urine albumin/creatinine ratio,UACR),UACR 均>30 mg/g 定义为蛋白尿[7]。胰岛素抵抗指数(insulin resistance index,IRI):空腹血糖(mmol/L)× 空腹胰岛素(mU/L)/22.5[8]。

1.2.2 认知功能测评 由经过规范化培训的一名专业人员采用 MoCA 量表对患者进行认知功能评估。此量表主要评估注意力、执行能力、语言、记忆、抽象思维、计算力和定向力。教育程度≤12 年总分加 1 分。总分共 30 分,总分<26 分为认知功能障碍,总分≥26 分为认知功能正常[9]。

1.3 统计学处理

应用 SPSS 19.0 统计软件对数据进行分析。符合正态分布的计量资料用均数±标准差($\bar{x}\pm s$)表示,组间比较采用 t 检验。不符合正态分布的计量资料以中位数(M)和四分位间距(Q_1, Q_3)表示,组间比较采用 Mann-Whitney U 检验。计数资料用例数(百分率)表示,组间比较用 χ^2 检验。多因素 logistic 回归分析认知功能障碍的危险因素。P<0.05 为差异有统计学意义。

2 结 果

2.1 2 组患者临床资料比较

2 组患者性别、糖尿病病程、HbA1c、UACR、IRI、CRP、IL-6、糖尿病视网膜病变、糖尿病神经病变比例等差异无统计学意义(P>0.05)。相比认知功能正常组,认知功能障碍组患者年龄、骨质疏松和 eGFR<60 ml/(min · 1.73 m^2)比例高,MoCA 分值和受教育时间低,差异均具有统计学意义(P<0.05;表 1)。

2.2 多因素 logistic 回归分析认知功能障碍的影响因素

以是否发生认知功能障碍为因变量,以组间比较有差异的因素为自变量,进行多因素 logistic 回归分析,结果显示,年龄(OR=1.05, 95%CI 1.01~1.10; P=0.011)和 eGFR<60 ml/(min · 1.73 m^2)[OR=2.15, 95%CI 1.08~4.26; P=0.029]为老年 2 型糖尿病患者认知功能障碍的独立危险因素。具体见表 2。

3 讨 论

本研究表明老年 2 型糖尿病患者认知功能障碍的患病率为 48.04%(98/204)。年龄和 eGFR<60 ml/(min · 1.73 m^2)是老年 2 型糖尿病患者认知功能障碍的独立危险因素。既往以 eGFR 为判定标准探索 CKD 与认知功能关系的研究结果并不一致。有研究结果表明 eGFR 低水平与认知功能下降或痴

表1 2组患者临床资料比较

Table 1 Comparison of clinical data between two groups

Item	Cognitive dysfuntion group (n=98)	Non-cognitive dysfunction group (n=106)	t/χ^2	P value
Age(years, $\bar{x}\pm s$)	68.4±7.7	66.0±6.7	−2.43	0.029
Gender(male/female, n)	51/47	63/43	1.13	0.288
Length of education(year, $\bar{x}\pm s$)	8.85±4.14	12.35±3.30	4.88	0.000
Duration of diabetes mellitus(year, $\bar{x}\pm s$)	14.60±9.15	15.57±8.37	0.79	0.429
BMI(kg/m^2, $\bar{x}\pm s$)	25.87±3.89	26.27±3.29	0.79	0.430
HbA1c(%, $\bar{x}\pm s$)	8.81±1.84	8.47±1.74	−1.36	0.176
TG(mmol/L, $\bar{x}\pm s$)	1.79±1.15	2.10±1.51	1.27	0.207
TC(mmol/L, $\bar{x}\pm s$)	4.36±1.06	4.23±0.96	−0.91	0.365
LDL-C(mmol/L, $\bar{x}\pm s$)	2.62±0.88	2.58±0.79	−0.37	0.711
HDL-C(mmol/L, $\bar{x}\pm s$)	1.18±0.34	1.10±0.28	−1.87	0.063
SCr(μmol/L, $\bar{x}\pm s$)	74.02±30.39	70.08±23.49	−1.03	0.304
UACR[mg/g, $M(Q_1, Q_3)$]	16.4(7.95,51.45)	16.1(8.65,65.80)	−0.75	0.454
eGFR[$ml/(min\cdot 1.73\,m^2)$, n(%)]				
≥90	43(43.87)	60(56.60)	3.30	0.069
60~89	29(29.60)	33(31.13)	0.01	0.936
<60	26(26.53)	13(12.26)	5.89	0.015
IRI[$M(Q_1, Q_3)$]	4.77(2.85,9.28)	4.97(2.19,8.95)	−0.66	0.511
CRP[mg/L, $M(Q_1, Q_3)$]	2.51(1.68,4.66)	2.46(1.69,4.21)	−0.06	0.949
IL-6[pg/ml, $M(Q_1, Q_3)$]	4.71(3.26,9.71)	3.87(2.44,7.96)	−1.83	0.067
MoCA(score, $\bar{x}\pm s$)	20.36±4.07	27.02±1.49	15.27	0.000
Diabetic neuropathy[n(%)]	36(36.73)	32(30.19)	0.89	0.345
Diabetic retinopathy[n(%)]	34(34.69)	37(34.91)	2.83	0.726
Osteoporosis[n(%)]	35(35.71)	21(19.81)	6.55	0.010

BMI: body mass index; HbA1c: glycosylated hemoglobin A1c; TG: triglycerides; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; SCr: serum creatinine; UACR: urine albumin/creatinine ratio; eGFR: estimated glomerular filtration rate; IRI: insulin resistance index; CRP: C-reactive protein; IL-6: interleukin-6; MoCA: Montreal Cognitive Assessment Scale.

表2 多因素logistic回归分析2型糖尿病患者认知功能障碍的危险因素

Table 2 Multivariate logistic regression analysis of risk factors associated with cognitive dysfunction of type 2 diabetes mellitus patients

Factor	B	SE	$Wald\ \chi^2$	OR(95%CI)	P value
Age	0.052	0.021	6.42	1.05(1.01−1.10)	0.011
eGFR<60 $ml/(min\cdot 1.73\,m^2)$	0.764	0.349	4.794	2.15(1.08−4.26)	0.029
Gender	0.106	0.308	0.119	1.12(0.61−2.03)	0.730
Osteoporosis	0.390	0.431	0.820	1.47(0.64−3.44)	0.365

eGFR: estimated glomerular filtration rate.

呆风险增加相关[10,11],而有的研究结果表明eGFR水平与认知功能并无关系[12,13]。CKD和认知功能障碍关系的确切机制目前尚不清楚。一方面可能原因是两种疾病有共同的血管危险因素,如糖尿病、高血压、高血脂等。而肾脏和大脑是终末器官,解剖和血流动力学相似,因此均易受血管危险因素损害[14]。研究表明两种疾病患者小血管疾病、脑白质变性、微出血患病率很高[15,16],而炎症、氧化应激、小血管疾病、脑白质变性也可能是导致认知功能障碍或痴呆的潜在机制[17,18]。另一方面是尿毒症的直接效应[17]。相比健康人,尿毒症患者大脑中认知区域相关毒素浓度约高10倍[19]。Ishimura等[20]研究结果显示,CKD是2型糖尿病患者出现心血管或脑血管疾病的危险因素,肾功能不全会加重动脉粥样硬化疾病进展,而心脑血管疾病与认知功能障碍显著相关。

与既往研究一致,本研究也表明年龄是认知功能障碍的独立危险因素。Launer等[21]的研究结果显示痴呆常发生在65~70岁,年龄每增加5岁,痴呆风险增加一倍。随着年龄增长,大脑逐渐退化,老年痴呆人群的大脑经常同时出现血管性和神经退行性改变。糖尿病患者较无糖尿病患者随年龄增长痴呆风险显著增加,可能原因是糖尿病患者合并大血管及微血管病变与认知功能障碍密切相关[22]。

总之,糖尿病患者认知功能障碍是多因素、多环节作用的结果,其病理生理机制尚未完全清楚。危

险因素包括血糖控制水平、胰岛素抵抗、糖基化终末产物(advanced glycation end products, AGEs)形成、糖尿病并发症、炎症介质等[22]。本研究未发现糖化血红蛋白水平、糖尿病并发症和炎症指标与认知功能障碍相关,主要原因可能是样本量小,未来需更大样本的研究去探索。同时本研究不能判断肾功能与认知功能障碍的因果关系,后期需前瞻性研究去证实。

综上所述,本研究表明年龄和 eGFR < 60 ml/(min · 1.73 m^2)与老年 2 型糖尿病患者认知功能障碍发生显著相关,提示 2 型糖尿病患者除了控制血压、血糖、血脂等,要注意监测 eGFR 水平,这将有助于预防糖尿病认知功能障碍的发生和进展。

【参考文献】

[1] Macisaac DJ, Ekinic EI, Jeruns G. Markers of and risk factors for the development and progression of diabetic kidney disease[J]. Am J Kidney Dis, 2014, 63(2): S39-S62. DOI: 10.1053/j.ajkd.2013.10.048.

[2] Etgen T, Chonchol M, Forstl H, *et al*. Chronic kidney disease and cognitive impairment: a systematic review and meta-analysis[J]. Am J Nephrol, 2012, 35(5): 474-482. DOI: 10.1159/000 338135.

[3] Deckers K, Camerino I, van Boxtel MP, *et al*. Dementia risk in renal dysfunction: a systematic review and meta-analysis of prospective studies[J]. Neurology, 2016, 88(2): 198-208. DOI: 10.121 2/WNL.0000000000003482.

[4] Kurella-Tamura M, Wadley V, Yaffe K, *et al*. Kidney function and cognitive impairment in US adults: The Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study[J]. Am J Kidney Dis, 2008, 52(2): 227-234. DOI: 10.1053/j.ajkd.2008.05.004.

[5] 康凯, 海舰, 王大鹏. 血管危险因素与老年认知功能障碍的研究进展[J]. 中华老年多器官疾病杂志, 2018, 17(12): 945-948. DOI: 10.11915/j.issn.1671-5403.2018.12.219.
Kang K, Hai J, Wang DP. Vascular risk factors and cognitive impairment in the elderly: a review[J]. Chin J Mult Organ Dis Elderly, 2018, 17(12): 945-948. DOI: 10.11915/j.issn.1671-5403.2018.12.219.

[6] Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus[J]. Diabet Med, 1998, 15(7): 539-553. DOI: 10.1002/(SICI)1096-9136(1998 07) 15:7<539::AID-DIA668>3.0.CO;2-S.

[7] Keane WF, Eknoyan G. Proteinuria, albuminuria, risk assessment, detection, elimination (PARADE): a position paper of the National Kidney Foundation[J]. Am J Kidney Dis, 1999, 33(5): 1004-1010.

[8] Matthews DR, Hosker JP, Rudenski AS, *et al*. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man[J]. Diabetologia, 1985, 28(7): 412-419.

[9] 温洪波, 张振馨, 牛富生, 等. 北京地区蒙特利尔认知量表的应用研究[J]. 中华内科杂志, 2008, 47(1): 36-39. DOI: 10.3321/j.issn:0578-1426.2008.01.012.
Wen HB, Zhang ZQ, Niu FS, *et al*. The application of Montreal cognitive assessment in urban Chinese residents of Beijing[J]. Clin J Intern Med, 2008, 47(1): 36-39. DOI: 10.3321/j.issn: 0578-1426.2008.01.012.

[10] Darsie B, Shlipak MG, Sarnak MJ, *et al*. Kidney function and cognitive health in older adults: the Cardiovascular Health Study[J]. Am J Epidemiol, 2014, 180(1): 68-75. DOI: 10.1093/aje/kwu102.

[11] Sasaki Y, Marioni R, Kasai M, *et al*. Chronic kidney disease: a risk factor for dementia onset: a population-based study. The Osaki-Tajiri Project[J]. J Am Geriatr Soc, 2011, 59(7): 1175-1181. DOI: 10.1111/j.1532-5415.2011.03477.x.

[12] O'Hare AM, Walker R, Haneuse S, *et al*. Relationship between longitudinal measures of renal function and onset of dementia in a community cohort of older adults[J]. J Am Geriatr Soc, 2012, 60(12): 2215 - 2222. DOI: 10.1111/j.1532-5415.2012.04238.x.

[13] Lipnicki DM, Sachdev PS, Crawford J, *et al*. Risk factors for late-life cognitive decline and variation with age and sex in the Sydney Memory and Ageing Study[J]. PLoS One, 2013, 8(6): e65841. DOI: 10.1371/journal.pone.0065841.

[14] Mogi M, Horiuchi M. Clinical interaction between brain and kidney in small vessel disease[J]. Cardiol Res Pract, 2011, 2011: 306189. DOI: 10.4061/2011/306189.

[15] Seliger SL, Sarnak MJ. Subclinical vascular disease of the brain in dialysis patients[J]. Am J Kidney Dis, 2007, 50(1): 8-10. DOI: 10.1053/j.ajkd.2007.04.022.

[16] Ikram MA, Vernooij MW, Hofman A, *et al*. Kidney function is related to cerebral small vessel disease[J]. Stroke, 2008, 39(1): 55-61. DOI: 10.1161/STROKEAHA.107.493494.

[17] Bugnicourt JM, Godefroy O, Chillon JM, *et al*. Cognitive disorders and dementia in CKD: the neglected kidney-brain axis[J]. J Am Soc Nephrol, 2013, 24(3): 353 - 363. DOI: 10.1681/ASN.2012050536.

[18] Madero M, Gul A, Sarnak MJ. Cognitive function in chronic kidney disease[J]. Semin Dial, 2008, 21(1): 29-37. DOI: 10.1111/j.1525-139X.2007.00384.x.

[19] De Deyn PP, Vanholder R, Eloot S, *et al*. Guanidino compounds as uremic (neuro) toxins[J]. Semin Dial, 2009, 22(4): 340-345. DOI: 10.1111/j.1525-139X.2009.00577.x.

[20] Ishimura E, Shoji T, Emoto M, *et al*. Renal insufficiency accelerates atherosclerosis in patients with type 2 diabetes mellitus[J]. Am J Kidney Dis, 2001, 38 (4 Suppl 1): S186-S190.

[21] Launer LJ, Andersen K, Dewey ME, *et al*. Rates and risk factors for dementia and Alzheimer's disease: results from EURODEM pooled analyses[J]. Neurology, 1999, 52(1): 78-84.

[22] Biessels GJ, Strachan MW, Visseren FL, *et al*. Dementia and cognitive decline in type 2 diabetes and prediabetic stages: towards targeted interventions[J]. Lancet Diabetes Endocrinol, 2014, 2(3): 246-255. DOI: 10.1016/S2213-8587(13)70088-3.

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