

血液透析患者不宁腿综合征相关影响因素分析

施颖颖 李冀军 宋岩 张健

【摘要】 目的 调查血液透析患者不宁腿综合征发病率并筛查其相关危险因素。方法 共 220 例维持性血液透析患者和 40 例慢性肾脏病患者,采用国际不宁腿综合征研究组评价量表(IRLS)评价不宁腿综合征严重程度,Beck 抑郁量表(BDI)评价抑郁症状,Epworth 嗜睡量表评价白天过度嗜睡,失眠严重程度指数(ISI)评价失眠程度。采用单因素和多因素前进法 Logistic 回归分析筛查血液透析患者发生不宁腿综合征的相关危险因素。结果 血液透析组病程($Z = -9.837, P = 0.000$)、血清铁蛋白($t = 2.847, P = 0.005$)、合并不宁腿综合征比例($\chi^2 = 10.918, P = 0.001$)、应用镇静催眠药比例($\chi^2 = 7.669, P = 0.006$)、IRLS 评分($t = 2.322, P = 0.020$)和 ISI 评分($Z = 4.117, P = 0.001$)均高于对照组。单因素和多因素前进法 Logistic 回归分析显示,糖尿病($OR = 3.387, 95\% CI: 1.538 \sim 7.461; P = 0.002$)、BDI 评分 > 9 分($OR = 2.643, 95\% CI: 1.457 \sim 4.795; P = 0.001$)和 ISI 评分 > 7 分($OR = 3.542, 95\% CI: 1.939 \sim 6.468; P = 0.000$)是血液透析患者发生不宁腿综合征的独立危险因素。结论 血液透析患者不宁腿综合征和失眠发病率较高,不宁腿综合征与失眠密切相关,抑郁症状在其中发挥重要作用。

【关键词】 血液透析滤过; 不宁腿综合征; 危险因素; 回归分析

Analysis of related factors for restless legs syndrome in hemodialysis patients

SHI Ying-ying, LI Ji-jun, SONG Yan, ZHANG Jian

Department of Nephrology, the First Affiliated Hospital of Chinese PLA General Hospital, Beijing 100048, China

Corresponding author: ZHANG Jian (Email: snowwolf-008@163.com)

【Abstract】 Objective To investigate the incidence of restless legs syndrome (RLS) in hemodialysis patients and to analyze the related risk factors. **Methods** There were 220 cases of hemodialysis as hemodialysis group and 40 cases of chronic nephrosis as control group. The severity of RLS was measured by International Restless Legs Syndrome Study Group Rating Scale (IRLS). Beck Depression Inventory (BDI) was used to evaluate the status of depression, Epworth Sleepiness Scale (ESS) was used to evaluate excessive daytime sleepiness (EDS), and Insomnia Severity Index (ISI) was used to evaluate the status of insomnia. Univariate and multivariate forward Logistic regression analysis was used to analyze the related risk factors for RLS in hemodialysis patients. **Results** In hemodialysis group duration ($Z = -9.837, P = 0.000$), serum ferritin ($t = 2.847, P = 0.005$), incidence rate of RLS ($\chi^2 = 10.918, P = 0.001$), the proportion of using hypnotic drugs ($\chi^2 = 7.669, P = 0.006$), IRLS ($t = 2.322, P = 0.020$) and ISI ($Z = 4.117, P = 0.001$) were significantly higher than control group. Univariate and multivariate forward Logistic regression analysis showed diabetes ($OR = 3.387, 95\% CI: 1.538-7.461; P = 0.002$), BDI > 9 score ($OR = 2.643, 95\% CI: 1.457-4.795; P = 0.001$) and ISI > 7 score ($OR = 3.542, 95\% CI: 1.939-6.468; P = 0.000$) were independent risk factors for RLS in hemodialysis patients. **Conclusions** Hemodialysis patients have a high incidence of RLS and insomnia. RLS is closely related with insomnia. Depression plays an important role therein.

【Key words】 Hemodiafiltration; Restless legs syndrome; Risk factors; Regression analysis

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作者单位:100048 北京,解放军总医院第一附属医院肾内科

通讯作者:张健(Email:snowwolf-008@163.com)

不宁腿综合征(RLS)是临床常见的感觉运动障碍性疾病,临床主要表现为夜间睡眠中出现双下肢极度不适感或疼痛,迫使患者不停移动下肢或下床行走^[1]。不宁腿综合征在正常人群中患病率为 0.1%~15.0%^[2-4],可以分为原发性和继发性不宁腿综合征,后者主要继发于铁缺乏、叶酸缺乏、妊娠、类风湿性关节炎和慢性肾病^[5-6],严重者甚至可以引起失眠、焦虑和抑郁^[7]。不宁腿综合征导致的神经性疼痛可以使睡眠质量下降,甚至出现失眠。血液透析患者常存在铁缺乏、微炎症反应状态,均可以导致不宁腿综合征^[8],并伴睡眠质量显著下降。本研究对解放军总医院第一附属医院行血液透析患者的不宁腿综合征发病率进行调查,并对其相关危险因素进行筛查。

资料与方法

一、临床资料

1. 纳入标准 (1)不宁腿综合征的诊断符合 2014 年国际不宁腿综合征研究组(IRLSSG)制定的标准^[9]。(2)规律血液透析时间>6 个月。(3)本研究经解放军总医院第一附属医院道德伦理委员会审核批准,所有患者或其家属均知情同意并签署知情同意书。

2. 排除标准 合并严重心脏、肺、肝脏疾病;合并神经系统疾病;合并脑血管病。

3. 一般资料 (1)血液透析组:选择解放军总医院第一附属医院 2014 年 1 月-2017 年 1 月进行维持性血液透析的患者 220 例,男性 102 例,女性 118 例;年龄 23~83 岁,平均为(50.32±14.23)岁;病程 1~16 年,中位病程 8(4,11)年;既往高血压病史 75 例(34.09%)、糖尿病病史 40 例(18.18%)、缺铁性贫血病史 13 例(5.91%);血清铁 6.60~55.20 μmol/L,平均为(15.11±4.62) μmol/L;血清铁蛋白 57.30~722.50 μg/L,平均(310.83±83.33) μg/L;其中 106 例(48.18%)合并不宁腿综合征;74 例(33.64%)服用镇静催眠药。(2)对照组:选择同期在我院肾内科住院治疗的 40 例慢性肾脏病且血清肌酐正常患者,男性 18 例,女性 22 例;年龄 19~72 岁,平均(49.70±13.47)岁;病程 0.50~3.00 年,中位病程 1.00(0.50,1.00)年;既往有高血压病史 12 例(30%)、糖尿病病史 6 例(15%);血清铁 10.60~27.80 μmol/L,平均(15.78±4.34) μmol/L;血清铁蛋白为 213.70~335.20 μg/L,平均(272.72±33.63) μg/L;其中 8 例

(20%)合并不宁腿综合征;5 例(12.50%)服用镇静催眠药。

二、研究方法

1. 临床资料采集 记录患者性别、年龄、病程、既往史(高血压、糖尿病、缺铁性贫血)、血清铁和铁蛋白水平、合并不宁腿综合征比例和应用镇静催眠药比例。

2. 量表评价 采用国际不宁腿综合征研究组评价量表(IRLS)^[10]评价不宁腿综合征严重程度,总评分为 40 分,评分 1~10 分为轻度,11~20 分为中度,21~30 分为严重,31~40 分为非常严重。采用 Beck 抑郁量表(BDI)评价抑郁症状,评分>9 分为存在抑郁症状。采用 Epworth 嗜睡量表(ESS)评价白天过度嗜睡(EDS)程度,总评分 24 分,评分 0~10 分,日间睡眠正常;11~12 分,日间睡眠为临界状态;13~24 分,白天过度嗜睡。采用失眠严重程度指数(ISI)^[11]评价失眠程度,总评分 28 分,评分 0~7 分,无意义的失眠;8~14 分,亚临床失眠;15~21 分,中度失眠;22~28 分,重度失眠。

3. 统计分析方法 采用 SPSS 18.0 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。呈正态分布的计量资料以均数±标准差($\bar{x}\pm s$)表示,采用两独立样本的 *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,采用 Mann-Whitney *U* 检验。血液透析患者不宁腿综合征相关危险因素的筛查采用单因素和多因素前进法 Logistic 回归分析。以 $P\leq 0.05$ 为差异具有统计学意义。

结 果

一、一般资料的比较

两组患者一般资料比较,性别、年龄、高血压、糖尿病、缺铁性贫血、血清铁以及 BDI 和 ESS 评分差异无统计学意义(均 $P>0.05$),血液透析组病程($P=0.000$)、血清铁蛋白($P=0.005$)、合并不宁腿综合征比例($P=0.001$)、应用镇静催眠药比例($P=0.006$)、IRLS 评分($P=0.020$)和 ISI 评分($P=0.001$)均高于对照组且差异有统计学意义(表 1)。根据是否合并糖尿病进一步行亚组分析,血液透析组中合并糖尿病患者不宁腿综合征发病率高于无糖尿病患者[72.50%(29/40)对 42.78%(77/180); $\chi^2=11.580, P=0.001$],对照组中合并糖尿病患者不宁腿综合征发病率与无糖尿病患者差异无统计学意义[1/6 对

表 1 两组患者临床资料的比较

Table 1. Comparison of general data between 2 groups

Item	Control (N = 40)	Hemodialysis (N = 220)	Statistic value	P value
Sex [case (%)]			0.250	0.874
Male	18 (45.00)	102 (46.36)		
Female	22 (55.00)	118 (53.64)		
Age ($\bar{x} \pm s$, year)	49.70 \pm 13.47	50.32 \pm 14.23	0.257	0.798
Duration [M (P_{25} , P_{75}), year]	1.00 (0.50, 1.00)	8.00 (4.00, 11.00)	-9.837	0.000
Hypertension [case (%)]	12 (30.00)	75 (34.09)	0.254	0.614
Diabetes [case (%)]	6 (15.00)	40 (18.18)	0.235	0.628
Iron-deficiency anemia [case (%)]	0 (0.00)	13 (5.91)	2.488	0.229
Serum iron ($\bar{x} \pm s$, $\mu\text{mol/L}$)	15.78 \pm 4.34	15.11 \pm 4.62	0.856	0.393
Serum ferritin ($\bar{x} \pm s$, $\mu\text{g/L}$)	272.72 \pm 33.63	310.83 \pm 83.33	2.847	0.005
RLS [case (%)]	8 (20.00)	106 (48.18)	10.918	0.001
Hypnotic drugs [case (%)]	5 (12.50)	74 (33.64)	7.669	0.006
IRLS ($\bar{x} \pm s$, score)	15.50 \pm 4.07	19.24 \pm 4.61	2.322	0.020
BDI ($\bar{x} \pm s$, score)	8.42 \pm 6.73	10.91 \pm 8.36	1.718	0.075
ESS [M (P_{25} , P_{75}), score]	1.00 (0.00, 3.00)	1.00 (0.00, 5.00)	1.904	0.610
ISI [M (P_{25} , P_{75}), score]	1.00 (0.00, 5.00)	4.00 (1.00, 11.00)	4.117	0.001

Two - independent - sample *t* test for comparison of age, serum iron, serum ferritin, IRLS and BDI, rank test for comparison of duration, ESS and ISI, and χ^2 test for comparison of others. RLS, restless legs syndrome, 不宁腿综合征; IRLS, International Restless Legs Syndrome Study Group Rating Scale, 国际不宁腿综合征研究组评价量表; BDI, Beck Depression Inventory, Beck 抑郁量表; ESS, Epworth Sleepiness Scale, Epworth 嗜睡量表; ISI, Insomnia Severity Index, 失眠严重程度指数

20.59% (7/34); $\chi^2 = 0.049, P = 0.825$]。

二、血液透析患者发生不宁腿综合征的相关危险因素

单因素 Logistic 回归分析显示, 糖尿病 ($P = 0.002$)、缺铁性贫血 ($P = 0.045$)、血清铁 $< 9 \mu\text{mol/L}$ ($P = 0.045$)、血清铁蛋白 $< 200 \mu\text{g/L}$ ($P = 0.035$)、BDI 评分 > 9 分 ($P = 0.001$) 和 ISI 评分 > 7 分 ($P = 0.000$) 是血液透析患者发生不宁腿综合征的相关危险因素 (表 2, 3); 将上述因素进一步代入多因素 Logistic 回归方程, 结果显示, 糖尿病 ($OR = 3.387, 95\% CI : 1.538 \sim 7.461; P = 0.002$)、BDI 评分 > 9 分 ($OR = 2.643, 95\% CI : 1.457 \sim 4.795; P = 0.001$) 和 ISI 评分 > 7 分 ($OR = 3.542, 95\% CI : 1.939 \sim 6.468; P = 0.000$) 是血液透析患者发生不宁腿综合征的独立危险因素

(表 4)。

讨 论

不宁腿综合征是血液透析患者的常见神经系统并发症, 对治疗效果和预后有不利影响, 使患者生活质量下降。研究显示, 不宁腿综合征可以显著增加尿毒症患者心脑血管事件和死亡风险^[12]。慢性肾脏病亦是继发性不宁腿综合征的重要原因, 血液透析患者不宁腿综合征发病率远远高于普通人群^[5]。有文献报道, 血液透析患者不宁腿综合征患病率为 6% ~ 50%^[13-14]。本研究血液透析患者不宁腿综合征发病率高达 48.18% (106/220), 远高于对照组, 与国外研究结果相一致。亦有文献报道, 血液透析患者常合并失眠^[15]。本研究血液透析患者血清铁蛋白、应用镇静催眠药比例、IRLS 评分和 ISI 评分均高于对照组, 与文献报道相一致。来自日本的研究显示, 血液透析患者不宁腿综合征与高磷血症和焦虑情绪有关^[16], 尽管发病机制尚不清楚, 但考虑与尿毒症毒素和微炎症反应状态有关, 因此, 维生素缺乏、贫血可能加重血液透析患者不宁腿综合征症状, 然而, 随着血液透析充分性的增加, 症状明显缓解。国内学者采用中医温阳通经柔筋缓急法治疗不宁腿综合征取得一定效果^[17]。

尽管血液透析患者不宁腿综合征发病率较高, 但相关影响因素尚不十分明确。在本研究中, 糖尿病是血液透析患者发生不宁腿综合征的独立危险因素。既往研究显示, 糖尿病合并多神经病变是不宁腿综合征的危险因素^[18]。除引起多神经病变外, 糖尿病还可以降低中脑和纹状体多巴胺水平, 影响中枢儿茶酚胺 (CA) 系统, 从而导致不宁腿综合征。在本研究中, ISI 评分 > 7 分是血液透析患者发生不宁腿综合征的独立危险因素。既往研究显示, 不宁腿综合征与失眠相关, 睡眠质量降低可以导致病死率增加, 从而引发精神错乱^[19-20]。Jaber 等^[8] 纳入 227 例血液透析患者, 其不宁腿综合征的预测因素包括男性、糖尿病、饮用咖啡、午后血液透析和腹膜透析。石理华等^[21] 认为, 年龄、体重指数 (BMI)、吸烟、透析充分性等均是血液透析患者发生不宁腿综合征的相关危险因素。Sagheb 等^[22] 的研究显示, 联合应用维生素 C 和维生素 E 可以缓解血液透析患者不宁腿综合征症状, 提示可能与血液透析丢失和摄入维生素不足有关。本研究未发现血清铁和铁蛋

表 2 血液透析患者不宁腿综合征相关危险因素变量赋值表

Table 2. Variable assignment table of risk factors for RLS in hemodialysis patients

Item	Assignment (score)	
	0	1
Sex	Male	Female
Age (year)	≤ 50	> 50
Duration (year)	≤ 8	> 8
Hypertension	No	Yes
Diabetes	No	Yes
Iron-deficiency anemia	No	Yes
Serum iron (μmol/L)	≥ 9	< 9
Serum ferritin (μg/L)	≥ 200	< 200
BDI (score)	≤ 9	> 9
ESS (score)	≤ 12	> 12
ISI (score)	≤ 7	> 7

BDI, Beck Depression Inventory, Beck 抑郁量表; ESS, Epworth Sleepiness Scale, Epworth 嗜睡量表; ISI, Insomnia Severity Index, 失眠严重程度指数

表 3 血液透析患者不宁腿综合征的单因素 Logistic 回归分析

Table 3. Univariate Logistic regression analysis of RLS in hemodialysis patients

Item	<i>b</i>	<i>SE</i>	Wald χ^2 value	<i>P</i> value	<i>OR</i> value	<i>OR</i> 95%CI
Sex	0.116	0.299	0.150	0.698	1.123	0.625- 2.017
Age	0.131	0.296	0.197	0.657	1.140	0.639- 2.036
Duration	0.489	0.278	3.090	0.079	0.613	0.355- 1.058
Hypertension	0.318	0.338	0.883	0.347	1.374	0.708- 2.666
Diabetes	1.268	0.411	9.543	0.002	3.555	1.590- 7.948
Iron-deficiency anemia	1.349	0.673	4.020	0.045	3.854	1.031-14.411
Serum iron	1.349	0.673	4.020	0.045	3.854	1.031-14.411
Serum ferritin	1.256	0.594	4.467	0.035	3.511	1.095-11.250
BDI	0.992	0.307	10.474	0.001	2.698	1.479- 4.921
ESS	0.311	0.630	0.243	0.622	1.365	0.397- 4.696
ISI	1.407	0.341	17.055	0.000	4.082	2.094- 7.958

BDI, Beck Depression Inventory, Beck 抑郁量表; ESS, Epworth Sleepiness Scale, Epworth 嗜睡量表; ISI, Insomnia Severity Index, 失眠严重程度指数

表 4 血液透析患者不宁腿综合征的多因素前进步 Logistic 回归分析

Table 4. Multivariate forward Logistic regression analysis of RLS in hemodialysis patients

Item	<i>b</i>	<i>SE</i>	Wald χ^2 value	<i>P</i> value	<i>OR</i> value	<i>OR</i> 95%CI
Diabetes	1.220	0.403	9.166	0.002	3.387	1.538- 7.461
Iron-deficiency anemia	0.507	1.421	0.127	0.721	1.660	0.102-26.901
Serum iron	0.838	1.357	0.853	0.367	4.245	0.349-37.629
Serum ferritin	1.739	1.277	1.853	0.173	5.689	0.465-69.524
BDI	0.972	0.304	10.211	0.001	2.643	1.457- 4.795
ISI	1.265	0.307	16.939	0.000	3.542	1.939- 6.468
Constant	-2.155	0.492	19.151	0.000		

BDI, Beck Depression Inventory, Beck 抑郁量表; ISI, Insomnia Severity Index, 失眠严重程度指数

白与不宁腿综合征相关,考虑与本研究铁剂使用率较高、贫血控制率较高有关。

血液透析患者常合并睡眠障碍,有研究显示,65%的血液透析患者合并睡眠障碍,主要表现为失眠^[23]。本研究血液透析组患者 ISI 评分高于对照组。Merlino 等^[24]纳入 883 例血液透析患者,失眠和不宁腿综合征比例分别为 68.97% (609/883) 和 18.46% (163/883)。抑郁情绪是临床常见的情感障碍,在血液透析患者中发生率为 25% ~ 50%^[25]。本

研究血液透析合并不宁腿综合征患者 BDI 和 ISI 评分均较高,提示抑郁和失眠与血液透析患者不宁腿综合征的发生有关,此类患者是否应予抗抑郁治疗,目前观点尚不统一。Unruh 等^[26]报告,合并严重不宁腿综合征的患者通常予苯二氮草类药物、抗抑郁药和抗癫痫药物以缓解临床症状、控制病情。

本研究结果显示,糖尿病、抑郁和失眠是血液透析患者发生不宁腿综合征的独立危险因素,针对上述危险因素的治疗是否可以降低血液透析患者不宁腿综合征发病率、改善预后尚待进一步深入研究。由于本研究是单中心研究,样本量较小,患者群体较单一,研究结果存在偏差,尚待进行多中心大样本临床研究进一步证实。

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