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## 心脏右向左分流对偏头痛患者临床症状的影响\*

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**摘要目的:**探讨心脏右向左分流(RLS)对偏头痛患者临床特征是否存在影响,并研究 RLS 分级与头痛强度之间的关系。**方法:**选择 2016 年 6 月-2018 年 12 月青岛大学附属医院收治的偏头痛患者 216 例作为偏头痛组,选择于青岛大学附属医院体检的健康志愿者 60 例作为对照组。216 例偏头痛患者根据有无 RLS 分为有 RLS 偏头痛组(127 例)和无 RLS 偏头痛组(89 例)。有 RLS 偏头痛患者根据 RLS 分级将其分为大分流组(n=51)、中分流组(n=11)和小分流组(n=65)。观察对照组与偏头痛组 RLS 情况,比较有 RLS 偏头痛组和无 RLS 偏头痛组患者的一般资料情况,比较大分流组、中分流组和小分流组患者的一般资料情况,采用多因素 Logistic 回归分析偏头痛患者产生 RLS 的危险因素。**结果:**对照组与偏头痛组小分流、中分流患病率比较差异无统计学意义( $P>0.05$ ),而偏头痛组大分流患病率高于对照组( $P<0.05$ )。有 RLS 偏头痛组患者的视觉先兆、感觉先兆的比例均大于无 RLS 偏头痛组,头痛初始年龄均小于无 RLS 偏头痛组,头痛强度均高于无 RLS 偏头痛组( $P<0.05$ ),两组患者年龄、性别、吸烟、饮酒、高血压、糖尿病、高血脂、运动先兆、遗传、头痛频率、头痛持续时间比较差异无统计学意义( $P>0.05$ )。不同 RLS 分级的偏头痛患者的视觉先兆、感觉先兆、头痛初始年龄、头痛强度整体比较差异有统计学意义( $P<0.05$ )。多因素 Logistic 回归分析显示,视觉先兆、感觉先兆、头痛初始年龄是偏头痛患者产生 RLS 的独立危险因素( $P<0.05$ )。**结论:**偏头痛发病年龄较小或有视觉先兆、感觉先兆可能提示偏头痛患者伴有 RLS,RLS 分级与头痛强度没有关系。

**关键词:**偏头痛;心脏右向左分流;经颅多普勒;临床特征;危险因素

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## Effect of Right-to-left Shunt on Clinical Symptoms of Migraine Patients\*

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**ABSTRACT Objective:** To investigate the influence of right-to-left shunt (RLS) on the clinical characteristics of migraine patients, and to study the relationship between RLS classification and headache intensity. **Methods:** 216 migraine patients admitted to the Affiliated Hospital of Qingdao University from June 2016 to December 2018 were selected as the migraine group, and 60 healthy volunteers in the Affiliated Hospital of Qingdao University were selected as the control group. 216 migraine patients were divided into RLS migraine group (127 cases) and non-RLS migraine group (89 cases) according to the presence or absence of RLS. Migraine patients with RLS were divided into large shunt group (n=51), medium shunt group (n=11) and small shunt group (n=65) according to RLS classification. The RLS was observed in control group and migraine group. The general data of migraine group with RLS and migraine group without RLS were compared. The general data of large shunt group, medium shunt group and small shunt group were compared. Multivariate Logistic regression analysis was used to analyze the risk factors of RLS in migraine patients. **Results:** There was no significant difference in the prevalence of small shunt and medium shunt between the control group and the migraine group ( $P>0.05$ ), while the prevalence of large shunt in the migraine group was higher than that in the control group ( $P<0.05$ ). The percentages of visual and sensory precursors in RLS migraine group were higher than those in non-RLS migraine group, initial age of headache was less than that in non-RLS migraine group, headache intensity was higher than that in non-RLS migraine group ( $P<0.05$ ). There was no significant difference in age, sex, smoking, alcohol consumption, hypertension, diabetes, hyperlipidemia, exercise precursors, heredity, frequency of headache and duration of headache between the two groups ( $P>0.05$ ). There were significant differences in visual precursors, sensory precursors, initial age of headache and headache intensity among migraine patients with different RLS classification ( $P<0.05$ ). Multivariate Logistic regression analysis showed that visual precursors, sensory precursors, initial age of headache were independent risk factors for RLS in migraine patients ( $P<0.05$ ). **Conclusion:** The younger age of migraine onset or visual and sensory precursors may indicate that migraine patients have RLS, RLS classification has no relationship with headache intensity.

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## 前言

偏头痛是指一侧或两侧颞部反复发作的搏动性头痛,疾病发作前可伴视觉、体觉先兆,常伴有呕吐现象<sup>[1,2]</sup>。若未能及时予以治疗,长期的偏头痛可引起失眠、记忆力减退,进而出现精神障碍、头痛频率加剧等现象<sup>[3,4]</sup>。由于偏头痛的具体发病机制目前尚不十分明确,故其治疗效果一直令人不太满意<sup>[5]</sup>。近年来,偏头痛与心脏右向左分流(right-to-left shunt, RLS)的关系逐渐引起了临床学者的重视<sup>[6,7]</sup>。RLS 主要是指来自右心的血液未经肺循环的充分氧合,并经过异常的血流通道进入左心的情况<sup>[8,9]</sup>。近年来越来越多文献<sup>[10,11]</sup>报道中国偏头痛患者(包括有先兆和无先兆偏头痛患者)RLS 患病率显著高于健康人群。然而,RLS 对偏头痛患者的临床特征是否有影响,目前尚不清楚。因此,本研究主要探讨 RLS 对偏头痛患者临床特征是否存在影响,并研究 RLS 分级与头痛强度之间的关系。

## 1 资料与方法

### 1.1 一般资料

选择 2016 年 6 月 -2018 年 12 月青岛大学附属医院收治的偏头痛患者 216 例作为偏头痛组。纳入标准:(1)符合第三版国际头痛疾病分类 - $\beta$  测试版有关偏头痛的诊断标准<sup>[12]</sup>;(2)患者都签署知情同意书。排除标准:(1)颞窗穿透不良者;(2)不能

建立静脉通路者;(3)严重颅内外血管狭窄者;(4)因严重心肺疾病不能配合 Valsalva 动作者。偏头痛组男 64 例,女 152 例,年龄 18-65 岁,平均(38.71 $\pm$  13.42)岁。选择于青岛大学附属医院体检的健康志愿者 60 例作为对照组,对照组男 18 例,女 42 例,年龄 21-63 岁,平均(41.27 $\pm$  13.86)岁。偏头痛组与对照组一般资料比较无统计学差异( $P>0.05$ ),组间可比。该研究经青岛大学附属医院伦理委员会批准。

### 1.2 方法

所有受试者行对比增强经颅多普勒超声(EMS-9A,德利凯,中国),取仰卧位,使用 2Hz 探头监测左侧大脑中动脉(middle cerebral artery, MCA)。通过三通管将两个 20 mL 注射器连接到 20G 套管针上,并在两个注射器之间交换 9 mL 盐水,1 mL 空气和 1 滴患者肘静脉血液的混合物 20 次,并使用均匀的造影剂很快就通过了肘静脉"弹丸式"。该过程进行三次:第一次静息状态下进行,监测微泡信号(microbubble, MB),判断平静呼吸下是否存在 RLS;第二、三次在运动状态下进行,每遍检查监测 20s,每遍间隔至少 5 min。对三次的结果进行评估,20s 内检测到最多的 MB 数量为 RLS 分流量的大小。基于使用单侧 MCA 监测在 TCD 光谱中检测到的 MB 的量来进行 RLS 分级的评估:小分流(<10MB),中分流(10-25MB)和大分流(>25 MB),见图 1。

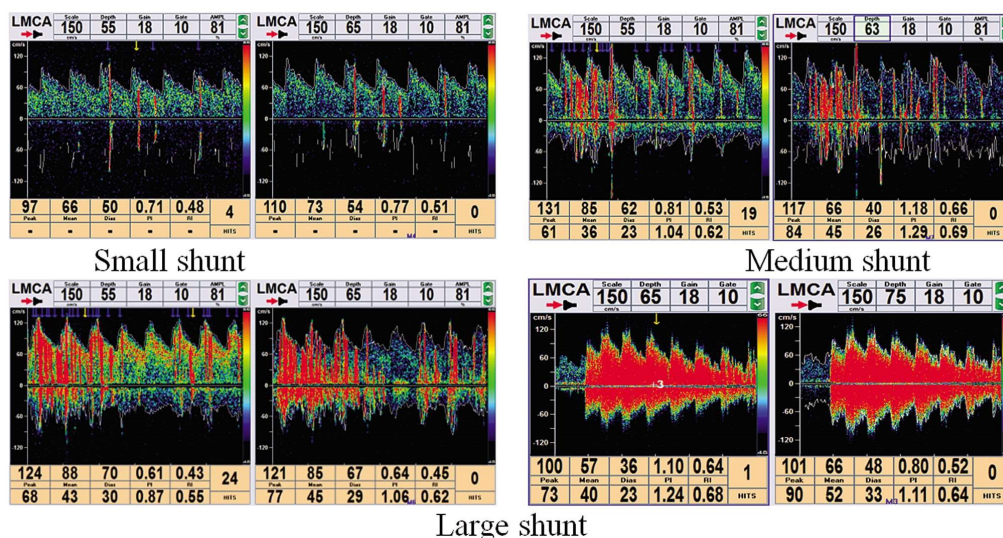


图 1 多普勒超声监测单侧大脑中动脉出现的 MB 数

Fig. 1 Doppler ultrasound monitoring MB number of unilateral middle cerebral artery

### 1.3 观察指标

记录偏头痛组患者一般资料情况,包括年龄、性别、吸烟、饮酒、高血压、糖尿病、高血脂、视觉先兆、感觉先兆、运动先兆、头痛初始年龄、遗传、头痛频率、头痛强度、头痛持续时间,其中头痛强度采用数字评分法进行评分<sup>[13]</sup>,分数 0~10 分,分数越高,疼痛感越强。(1)观察对照组与偏头痛组 RLS 情况。(2)216 例偏头痛患者根据有无 RLS 分为有 RLS 偏头痛组(127 例)和

无 RLS 偏头痛组(89 例),比较有 RLS 偏头痛组和无 RLS 偏头痛组患者的一般资料情况。(3)有 RLS 偏头痛患者根据 RLS 分级将其分为大分流组(n=51)、中分流组(n=11)和小分流组(n=65),比较大分流组、中分流组和小分流组患者的一般资料情况。(4)采用多因素 Logistic 回归分析偏头痛患者产生 RLS 的危险因素。

### 1.4 统计学方法

统计分析使用 SPSS 24.0 进行,采用[n(%)]表示计数资料,实施  $\chi^2$  检验,采用( $\bar{x} \pm s$ )表示计量资料,实施 t 检验,采用多因素 Logistic 回归分析偏头痛患者产生 RLS 的危险因素。检验水准  $\alpha=0.05$ 。

## 2 结果

### 2.1 对照组与偏头痛组 RLS 情况比较

偏头痛组 RLS 患病率为 58.79%(127/216),对照组 RLS 患病率为 28.33%(17/60),对照组与偏头痛组小分流、中分流患病率比较差异无统计学意义( $P>0.05$ ),而偏头痛组大分流患病率高于对照组( $P<0.05$ ),见表 1。

表 1 对照组与偏头痛组 RLS 情况比较[n(%)]

Table 1 Comparison of RLS between control group and migraine group[n(%)]

Groups	n	Small shunt	Medium shunt	Large shunt
Control group	60	12(20.00%)	2(3.33%)	3(5.00%)
Migraine group	216	65(30.09%)	11(5.09%)	51(23.61%)
$\chi^2$		2.318	0.324	10.335
P		0.123	0.569	0.001

### 2.2 有 RLS 偏头痛组和无 RLS 偏头痛组患者的单因素分析

有 RLS 偏头痛组患者的视觉先兆、感觉先兆的比例均大于无 RLS 偏头痛组,头痛初始年龄均小于无 RLS 偏头痛组,头

痛强度均高于无 RLS 偏头痛组( $P<0.05$ );两组患者年龄、性别、吸烟、饮酒、高血压、糖尿病、高血脂、运动先兆、遗传、头痛频率、头痛持续时间比较差异无统计学意义( $P>0.05$ ),见表 2。

表 2 有 RLS 偏头痛组和无 RLS 偏头痛组患者的单因素分析

Table 2 Univariate analysis of patients with RLS migraine group and non-RLS migraine group

Variable	RLS migraine group(n=127)	Non-RLS migraine group(n=89)	$\chi^2/t$	P
Age(years old)	38.92± 8.93	38.87± 7.26	0.044	0.965
Gender(Male/Female)	31/96	28/61	1.310	0.252
Smoking	13(10.24)	9(10.11)	0.001	0.976
Alcohol Consumption	13(10.24)	10(11.24)	0.055	0.815
Hypertension	9(7.09)	4(4.49)	0.622	0.430
Diabetes	5(3.94)	2(2.25)	0.477	0.490
Hyperlipidemia	8(6.30)	5(5.62)	0.043	0.846
Visual precursors	36(28.35)	10(11.24)	9.140	0.003
Sensory precursors	16(12.60)	2(2.25)	7.340	0.007
Exercise precursors	9(7.09)	2(2.25)	3.143	0.076
Initial age of headache(years old)	25.38± 11.56	29.93± 12.91	2.713	0.007
Heredity	23(18.11)	25(28.09)	3.015	0.082
Frequency of headache	4.64± 0.54	4.61± 0.56	0.396	0.693
Headache intensity(scores)	5.93± 1.52	5.05± 1.41	4.314	0.000
Duration of headache(d)	10.91± 2.62	11.22± 3.51	0.743	0.358

### 2.3 不同 RLS 分级的偏头痛患者的一般资料比较

不同 RLS 分级的偏头痛患者的视觉先兆、感觉先兆、头痛初始年龄、头痛强度整体比较差异有统计学意义( $P<0.05$ ),见表 3。

### 2.4 偏头痛患者产生 RLS 的危险因素分析

以偏头痛患者产生 RLS 为因变量(有 =1,无 =0),以表 2 中的有统计学差异的指标为自变量进行多因素 Logistic 回归模型分析,结果显示:视觉先兆、感觉先兆、头痛初始年龄是偏头痛患者产生 RLS 的独立危险因素( $P<0.05$ ),见表 4。

## 3 讨论

偏头痛和 RLS 之间的潜在机制仍然不清楚,目前提出了几种潜在机制理论,偏头痛的化学触发因素,例如血清素,通常由肺循环灭活,可通过 RLS 绕过肺循环过滤器并进入脑循环,导致偏头痛的发作<sup>[14,15]</sup>。5-羟色胺也可以从血小板中释放出来,血小板可以通过剪切应力激活并释放血清素,最终导致偏头痛发作,这可能由心脏卵圆孔未闭引发<sup>[16,17]</sup>。反常栓子已被提出作为偏头痛的触发因素,微小栓子,例如小静脉血凝块和血小板

表 3 不同 RLS 分级的偏头痛患者的一般资料比较

Table 3 Comparison of general data of migraine patients with different RLS classification

Variable	Small shunt group( n=65)	Medium shunt group( n=11)	Large shunt group( n=51)	$\chi^2/t$	P
Visual precursors	11(16.92)	4(36.36)	21(41.18)	8.663	0.013
Sensory precursors	3(4.62)	3(27.27)	10(19.61)	6.219	0.045
Initial age of headache(years old)	27.86± 3.54	25.63± 3.08	22.16± 2.95	19.362	0.000
Headache intensity(scores)	5.41± 0.96	6.02± 1.06	6.57± 0.82	20.635	0.000

表 4 偏头痛患者产生 RLS 的危险因素分析

Table 4 Risk factors for RLS in migraine patients

Variable	Regression coefficient	Standard error	Wald $\chi^2$	P	OR	95%CI
Visual precursors	1.185	0.418	6.419	0.017	1.576	1.032~6.574
Sensory precursors	1.077	0.367	5.796	0.021	2.374	1.173~4.618
Initial age of headache	1.012	0.715	12.656	0.000	4.391	2.653~15.794

聚集,通常被捕获在肺中,并且当通过 RLS 引入动脉循环时可以作为偏头痛的潜在触发因素<sup>[18,19]</sup>。此外,动物实验已经表明<sup>[20,21]</sup>,微栓子通过诱导皮质扩散抑制引起偏头痛发作。短暂的缺氧事件也用于解释偏头痛和 RLS 之间的机制,当脱氧的静脉血进入并通过 RLS 与含氧动脉血结合时发生,低氧血症也被证明是皮质扩散抑制的潜在诱因<sup>[22,23]</sup>。

本研究结果显示,偏头痛组中 RLS 的患病率显著高于对照组,偏头痛组大分流的患病率明显高于对照组。偏头痛与 RLS 密切相关,尤其是大分流,偏头痛和 RLS 之间的密切关联意味着 RLS 在偏头痛中可能起着重要的作用<sup>[24]</sup>。在本研究中,RLS 分级与偏头痛患者头痛的临床参数之间没有关联,分流程度与头痛的临床参数无关可能表明 RLS 与偏头痛之间的关联机制不仅与分流程度有关,还与剪切应力有关<sup>[25]</sup>。Sadrameli SS 等人<sup>[26]</sup>假设更大程度的 RLS 将更多的化学触发因素,反常栓子和静脉脱氧血红蛋白转移到全身循环,引起偏头痛发作。相反,当血液通过心内和心脏分流时,小程度的 RLS 更可能激活血小板属于剪切应力,从而释放血清素并诱导偏头痛发作<sup>[27,28]</sup>。本研究结果还显示,偏头痛患者发生 RLS 与视觉先兆、感觉先兆、头痛初始年龄、头痛强度等息息相关,头痛初始年龄越低,偏头痛患者长期分流的时间则越长,且长期的治疗效果差,致使其头痛强度逐日递增。此外,与没有 RLS 的偏头痛患者相比,患有 RLS 的偏头痛患者的视觉先兆和感觉先兆的患病率明显更高,这种现象可能与矛盾栓子有关<sup>[29,30]</sup>。进一步的因素 Logistic 回归分析显示,视觉先兆、感觉先兆、头痛初始年龄是偏头痛患者产生 RLS 的独立危险因素,临床可对上述情况进行密切关注,以对早期偏头痛患者作出更为准确的诊断。

综上所述,偏头痛与 RLS 密切相关,特别是大分流。本研究建议,当患者表现出偏头痛发病年龄较小或伴有以下临床特征(包括视觉先兆,感觉先兆和偏头痛症状在过去 12 个月内恶化)时,可建议偏头痛患者接受 RLS 检查,分流程度与头痛临床参数无显著差异。

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