

doi: 10.13241/j.cnki.pmb.2021.23.014

血清 miR-200a 和 S-100B 与妊娠期高血压疾病患者临床参数的关系及诊断价值分析*

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摘要 目的:检测妊娠期高血压疾病(HDCP)患者血清 miR-200a 和 S-100 钙结合蛋白 B(S-100B)水平,分析其与 HDCP 患者临床参数的关系及对 HDCP 的诊断价值。**方法:**检测 2017 年 2 月至 2019 年 2 月我院收治的 182 例 HDCP 患者(观察组)和 153 例健康孕妇(对照组)血清 miR-200a、S-100B 水平,并比较不同年龄、入组时体质量指数(BMI)、分娩孕周、孕次、产次、病情程度、预后的 HDCP 患者血清 miR-200a、S-100B 水平差异。Pearson 相关性分析血清 miR-200a、S-100B 及有关指标间的相关性。受试者工作特征(ROC)曲线分析血清 miR-200a、S-100B 水平诊断 HDCP 的价值。**结果:**观察组血清 miR-200a、S-100B 水平均高于对照组($P<0.05$),血清 miR-200a、S-100B 水平随着病情加重而升高($P<0.05$)。血清 miR-200a 水平与 HDCP 患者年龄、入组时 BMI、预后有关($P<0.05$),血清 S-100B 水平与 HDCP 患者分娩孕周、预后有关($P<0.05$)。Pearson 相关分析结果显示,HDCP 患者血清 miR-200a 与 S-100B、年龄、入组时 BMI 呈正相关($P<0.05$),血清 S-100B 与分娩孕周呈正相关($P<0.05$)。ROC 分析结果显示,血清 miR-200a、S-100B 水平诊断 HDCP 的曲线下面积(AUC)分别为 0.743、0.721,灵敏度和特异度分别为 72.93%、74.59%、72.00%、75.00%。**结论:**HDCP 患者血清 miR-200a、S-100B 水平升高,两者与 HDCP 发病、进展和预后均存在密切关系。miR-200a、S-100B 可能作为辅助 HDCP 诊断的生物学指标。

关键词:妊娠期高血压疾病;miR-200a;S-100B;病情;诊断

中图分类号:R714.246 文献标识码:A 文章编号:1673-6273(2021)23-4467-05

Analysis of the Relationship between Serum mir-200a and S-100B and Clinical Parameters in Hypertensive Disorders Complicating Pregnancy and Their Diagnostic Value*

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ABSTRACT Objective: To detection the expression characteristics of serum mir-200a and s-100 calcium-binding protein B(S-100B) in patients with hypertensive disorders complicating pregnancy (HDCP), and analyze the relationship between miR-200a and S-100B in patients with HDCP, and its diagnostic value for HDCP. **Methods:** The serum miR-200a and S-100B levels of 182 HDCP patients (observation group) and 153 healthy pregnant women (control group) admitted to our department of obstetrics and gynecology from February 2017 to February 2019 were detected. The differences of serum miR-200a and S-100B in patients with HDCP were compared at different ages, body mass index (BMI) at enrollment, gestational week, gestation time, birth time, disease severity and prognosis. Pearson correlation analysis of serum miR-200a, S-100B and correlation between related indexes, and receiver operator characteristics curve (ROC) was used to analyze the value of serum miR-200a and S-100B levels in diagnosing HDCP. **Results:** Serum miR-200a and S-100B levels in the observation group were higher than those in the control group ($P<0.05$). The levels of serum miR-200a and S-100B increased with the aggravation of the disease ($P<0.05$). Serum miR-200a level was associated with age, BMI at enrollment and prognosis of HDCP patients ($P<0.05$), and serum S-100B level was associated with gestational age and prognosis of HDCP patients ($P<0.05$). Pearson correlation analysis showed that serum miR-200a was positively correlated with S-100B, age and BMI at enrollment in patients with HDCP ($P<0.05$), Serum S-100B was positively correlated with gestational age ($P<0.05$). ROC analysis showed that the AUC of serum miR-200a and S-100B in HDCP diagnosis was 0.743 and 0.721 respectively, and the sensitivity and specificity were 72.93%, 74.59%, 72.00%, 75.00% respectively. **Conclusion:** The serum miR-200a and S-100B levels of HDCP patients were increased, which were closely related to the incidence, progression and prognosis of HDCP. MiR-200a and S-100B can be used as valuable biological indicators for HDCP diagnosis.

Key words: Hypertensive disorders complicating pregnancy; miR-200a; S-100B; Illness; Diagnosis

* 基金项目:江苏省科技发展计划项目(BE2017610)

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(收稿日期:2021-04-10 接受日期:2021-04-30)

Chinese Library Classification(CLC):R714.246 Document code: A

Article ID: 1673-6273(2021)23-4467-05

前言

妊娠期高血压疾病(HDCP)是孕产妇围产期死亡的主要原因之一,发病率5.2%~8.2%^[1],HDCP严重危害母婴安全,导致不良妊娠结局风险增加,但关于其发病机制尚不明确^[2]。miR-200a是微小非编码单链RNA成员之一,参与炎症反应调节、细胞分化增殖、癌细胞增殖迁移等多种生理过程^[3,4],有研究显示高水平miR-200a与HDCP发病相关^[5,6]。S-100钙结合蛋白B(S-100B)由星形胶质细胞产生,是脑损伤的敏感指标^[7],近年来有研究显示S-100B参与HDCP的发病^[8]。本研究对182例HDCP患者血清miR-200a和S-100B水平进行监测,分析其与HDCP患者临床参数的关系及对HDCP的诊断价值。

1 资料与方法

1.1 临床资料

选择2017年2月至2019年2月我院收治的182例HDCP患者(观察组),纳入标准:①符合《妇产科学》第8版中HDCP诊断标准^[9];②经超声诊断单活胎妊娠;③既往无经临床诊断的高血压、糖尿病。排除标准:①妊娠期同时合并糖尿病、支原体感染、风疹感染、巨细胞感染等;②经超声诊断双胎或多胎妊娠;③合并自身免疫疾病、脑炎、颅内肿瘤、癫痫等。患者年龄21~39岁,平均(35.65±2.31)岁;分娩孕周34~39周,平均(36.91±1.01)周;入组时体质量指数(BMI)23~29 kg/m²,平均(27.03±1.41)kg/m²;孕次0~6次,平均(2.21±0.52)次;产次0~4次,平均(2.53±0.61)次。根据HDCP分类标准^[9]将观察组分为三个亚组:妊娠高血压组(HDP组)[收缩压≥140 mmHg和(或)舒张压≥90 mmHg,尿蛋白(-)]63例、轻度子痫前期组[收缩压≥140 mmHg和(或)舒张压≥90 mmHg,蛋白尿≥0.3 g/24h或随机尿蛋白(+)]65例、重度子痫前期组[血压和蛋白尿持续升高,发生母体脏器功能不全或胎儿并发症]54例。另随机选择同期于我院产科行规律围产保健的153例健康孕妇为对照组,均为单胎妊娠,足月生产,并经系统产检排除妊娠期并发症和合并症,年龄20~39岁,平均(35.74±2.43)岁;分娩孕周36~40周,平均(38.23±1.43)周,入组时BMI 22~27 kg/m²,平均(25.06±1.49)kg/m²,孕次0~5次,平均(2.16±0.47)次;产次0~3次,平均(2.11±0.44)次,观察组和对照组年龄、孕次、产次比较差异无统计学意义($P>0.05$),观察组入组时BMI大于对照组($P<0.05$),分娩孕周小于对照组($P<0.05$)。本研究获得我院医学伦理委员会批准,孕妇及其家属均签署同意书。

1.2 方法

(1)血清miR-200a检测:所有受试者均于入组时采集空腹肘静脉血5 mL,注入EDTA抗凝管,4℃、2 000 r/min于TDZ4-WS低速自动平衡离心机(长沙湘智离心机仪器有限公司)离心10 min,取血清-80℃保存。取血清样本,TRIzol法(TRIzol试剂盒购自美国Invitrogen公司)按照说明书流程提取总RNA,选择吸光度>1.8的RNA(NanoDrop公司生产的ND-1000紫外分光光度计检测)20 μg,M-MLV逆转录酶

(Epicentre公司)逆转录为cDNA,反应条件:15℃ 30 min,45℃ 30 min,85℃ 5 min灭活。CFX96实时荧光PCR仪(美国BioRad公司),取cDNA样品加入qRT-PCR反应体系[0.4 μL PCR引物F(10 μmol/L),0.4 μL PCR引物R(10 μmol/L),1 μL PCR缓冲液(10×),1 μL dNTP(2.5 mmol/L),0.6 μL氯化镁溶液,0.5 U Taq聚合酶,0.2 μL ROX Reference Dye,2.5 μmol/L荧光染料 Syber green I,加水至8 μL],反应条件:95℃变性15 s,65℃退火20 s,75℃延伸15 s,共40个循环。引物购自金域医学检验中心,序列如下:miR-200a,上游:5'CGGGT-GAAAT-GTTTAGG3',下游:5'TTGCCATGTGTACGTA3',U6(内参):上游:5'GCTT CGGCAGCACATATACTAAAAT-3',下游5'CGCTTC ACGAA TTTGCGTGTTCAT-3'。2^{-ΔΔCt}计算miR-200a相对表达量,取3次平均值。(2)血清S-100B水平检测:所有受试者均于入组时采集空腹肘静脉血5 mL,离心方式同上,以HED-SY96S全自动酶标仪(山东霍尔德电子科技有限公司)采用酶联免疫吸附法检测血清S-100B水平,试剂盒购自上海瓦兰生物科技有限公司。(3)预后:所有患者均追踪母婴结局,统计子痫发作、产后出血、孕产妇死亡、胎儿宫内生长发育受限、新生儿窒息、新生儿死亡等不良妊娠结局发生情况,将发生不良妊娠结局者归为预后不良,共42例,未发生不良妊娠结局者归为预后良好,共140例。

1.3 统计学分析

使用SPSS22.0进行研究资料分析。计量数据经D-W检验符合正态分布,以MEAN±SD描述,比较采用独立样本t检验或单因素方差分析(两两比较LSD-t检验)。计数资料以例(率)描述,予以卡方检验。指标间相关分析为Pearson相关检验。受试者工作特征(ROC)曲线分析miR-200a、S-100B诊断HDCP的价值。检验水准 $\alpha=0.05$ 。

2 结果

2.1 血清miR-200a和S-100B水平比较

观察组、HDP组、轻度子痫前期组、重度子痫前期组血清miR-200a、S-100B水平均高于对照组($P<0.05$),观察组血清miR-200a、S-100B水平随着病情加重而升高($P<0.05$),见表1。

2.2 血清miR-200a和S-100B水平与HDCP患者临床参数的关系

不同年龄、入组时BMI、预后的HDCP患者血清miR-200a水平差异有统计学意义($P<0.05$),不同分娩孕周、孕次、产次的HDCP患者血清miR-200a水平差异无统计学意义($P>0.05$);不同分娩孕周、预后的HDCP患者血清S-100B水平差异有统计学意义($P<0.05$),不同年龄、入组时BMI、孕次、产次的HDCP患者血清S-100B水平差异无统计学意义($P>0.05$),见表2。

2.3 HDCP患者血清miR-200a与S-100B及其各因素的相关性分析

Pearson相关分析结果显示,HDCP患者血清miR-200a与S-100B、年龄、入组时BMI呈正相关($r=0.402,0.421,0.384$,均

$P=0.000$),血清 S-100B 与分娩孕周呈正相关($r=0.410, P=0.000$)。

表 1 血清 miR-200a、S-100B 水平比较 ($\bar{x}\pm s$)
Table 1 Comparison of serum miR-200a and S-100B levels ($\bar{x}\pm s$)

Groups	n	miR-200a	S-100B($\mu\text{g/L}$)
Control group	153	0.52±0.13	0.09±0.01
Observation group	182	1.21±0.36 ^a	0.13±0.05 ^a
HDP group	63	1.04±0.22 ^a	0.11±0.03 ^a
Mild preeclampsia group	65	1.20±0.32 ^{ab}	0.13±0.06 ^{ab}
Severe preeclampsia group	54	1.43±0.39 ^{abc}	0.16±0.09 ^{abc}

Note: compared with the control group, ^a $P < 0.05$; compared with HDP group, ^b $P < 0.05$; compared with mild preeclampsia group, ^c $P < 0.05$.

表 2 血清 miR-200a 和 S-100B 水平在不同 HDCP 患者临床参数间的比较 ($\bar{x}\pm s$)
Table 2 Comparison of serum miR-200a and S-100B levels among clinical parameters of different HDCP patients ($\bar{x}\pm s$)

Clinical parameters	n	miR-200a	t	P	S-100B($\mu\text{g/L}$)	t	P
Age							
≥ 35 years old	102	1.26±0.34	2.769	0.006	0.13±0.06	0.273	0.786
<35years old	80	1.15±0.21			0.13±0.03		
BMI into the group							
≥ 25kg/m ²	96	1.27±0.35	2.902	0.004	0.13±0.05	0.608	0.544
<25kg/m ²	86	1.14±0.22			0.13±0.03		
Gestational weeks of delivery							
≥ 36weeks	106	1.20±0.31	0.603	0.547	0.11±0.06	4.053	0.001
<36weeks	76	1.22±0.25			0.14±0.02		
Times of pregnancies							
≥ 3times	76	1.22±0.33	0.368	0.713	0.13±0.06	0.551	0.583
<3times	106	1.20±0.29			0.13±0.04		
Parity							
≥ 3times	53	1.22±0.36	0.294	0.769	0.13±0.02	0.327	0.744
<3times	129	1.20±0.35			0.13±0.07		
Prognosis							
Good	140	0.90±0.21	7.485	0.000	0.09±0.03	5.141	0.000
Bad	42	1.30±0.33			0.14±0.06		

2.4 血清 miR-200a、S-100B 对 HDCP 的诊断价值分析

ROC 曲线分析显示 miR-200a、S-100B 诊断 HDCP 的曲线下面积 (area under the curve, AUC) 分别为 0.743 (95%CI: 0.682~0.804)、0.721 (95%CI: 0.660~0.782)。约登指数最大值对应的 miR-200a、S-100B 值为 HDCP 的截断点分别为 1.021、0.115 $\mu\text{g/L}$, 该界值下诊断 HDCP 的灵敏度和特异度分别为

72.93%、74.59%;72.00%、75.00%,见表 3、图 1。

3 讨论

HDCP 是危害全球女性和婴幼儿健康的公共卫生问题之一,妊娠期糖尿病、肥胖、早产或多胎,孕妇年龄小于 20 岁或大于 35 岁、血栓形成均可能导致 HDCP 风险增加^[10,11]。HDCP 严

表 3 血清 miR-200a、S-100B 诊断 HDCP 的效能
Table 3 Diagnostic efficiency of serum miR-200a and S-100B for HDCP

Index	Sensitivity(%)	Specificity(%)	Yoden index	Positive predictive value(%)	Negative predictive value(%)	Diagnostic coincidence rate(%)
miR-200a	72.93	72.00	0.4493	82.50	59.02	72.60
S-100B	74.59	75.00	0.4959	84.38	61.48	74.47

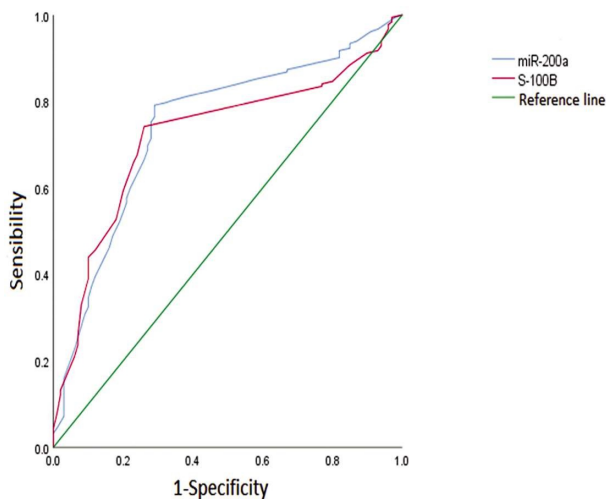


图1 血清 miR-200a、S-100B 诊断 HDCP 的 ROC 曲线图

Fig.1 ROC curve of serum miR-200a and S-100B in the diagnosis of HDCP

重影响孕妇、胎儿生命健康和新生儿结局,孕妇表现为子痫前期,剖宫产和早产,胎儿表现为宫内发育迟缓、宫内窘迫或死亡,新生儿表现为出生体重低于 2500 g 或围产期死亡^[12,13]。HDCP 发病至确诊时间较长,目前 HDCP 诊断多依靠临床表现、体征、血压/尿蛋白监测等,当发现蛋白尿时已经处于子痫前期,因此寻找可靠、有效的生物学标志物已成为围产科学研究的热点。

miRNA 是转录后调控网络的核心调控因子,广泛参与机体几乎所有的生理和病理活动调节过程^[14-16]。miR-200a 是 miR-200 家族成员,通过 5' 末端种子序列识别、配对靶基因 mRNA 3'UTR 部分碱基,负性调控基因表达^[17-19]。本研究发现 HDCP 组患者血清 miR-200a 异常高表达,胎盘发育过程中滋养细胞侵袭不足是导致 HDCP 发病的主要机制,内分泌腺源性血管内皮生长因子(EG-VEGF)是促进胎盘滋养细胞侵袭的关键因子,EG-VEGF 与初级纤毛结合启动信号级联,促进胎盘发育。miR-200a 过表达可抑制 EG-VEGF、基质金属蛋白酶-9 表达,阻断下游细胞外信号调节激酶信号,导致滋养层着床不足。本研究发现 miR-200a 在重度子痫前期、不良预后患者表达水平明显增高,说明 miR-200a 过表达与 HDCP 患者病情和预后有关,高水平 miR-200a 预示着 HDCP 病情加重和不良预后的可能。高龄、肥胖是 HDCP 发病的高危因素^[20,21],且 miR-200a 在 HDP 发病机制中与 HDCP 高危因素可能发挥相互作用机制,促使了 HDCP 发病和病情进展。

S-100B 广泛分布于星形胶质细胞内,在内源性或外源性神经损伤时大量从胶质细胞释放并经血脑屏障入血^[22-24]。脑损伤和 HDCP 均存在血管痉挛、内皮损伤、局部缺血改变,推测 S-100B 与 HDCP 可能存在相关性^[25-27]。本研究 HDCP 组患者血清 S-100B 水平高于对照组,可能的机制为:HDCP 患者全身小动脉痉挛导致脑血管过度收缩,颅内压增高损伤脑神经,引起 S-100B 的释放增加,S-100B 通过血脑屏障进入血液循环,血清 S-100B 浓度升高^[28-30]。同时 HDCP 患者存在滋养细胞凋亡现象,S-100B 在细胞凋亡中发挥重要作用,S-100B 胎盘组织有一定的表达,其水平随着滋养层凋亡细胞逐渐增加^[31-33],提示

S-100B 可能通过参与胎盘滋养细胞的凋亡参与子痫前期的发病过程。本研究观察血清 S-100B 水平与 HDCP 病情程度、分娩孕周相关,一项队列研究同样显示子痫前期患者妊娠 37 周时血清 S-100B 水平与正常孕妇差异较妊娠 33 周更明显^[34]。本研究血清 S-100B 水平在不良预后 HDCP 患者中表达较高,提示 S-100B 与 HDCP 患者母婴结局有关,S-100B 水平越高预示着胎盘功能越差,HDCP 病情更为严重,发生不良妊娠结局的可能性更大。ROC 分析结果说明 miR-200a、S-100B 诊断 HDCP 具有一定准确性,临床可通过监测妊娠早期血清 miR-200a、S-100B 水平,有助于发现疑似 HDCP 患者。本研究相关性分析 miR-200a、S-100B 呈正相关,提示 miR-200a、S-100B 在 HDCP 发病和病情进展中可能发挥协同作用机制,共同促使 HDCP 的发病,但是具体机制尚不清楚,尚待更多临床和基础研究加以证实。

综上,HDCP 患者血清 miR-200a、S-100B 水平升高,miR-200a、S-100B 在 HDCP 发病、进展过程中发挥协同作用机制,与 HDCP 发病、进展和预后均存在密切关系,可作为 HDCP 诊断的有价值生物学指标。

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