

冠心病并发幽门螺杆菌感染患者血清 HP抗体谱特征与炎性因子水平相关性分析^{*}

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摘要:目的 探讨冠心病(CHD)并发幽门螺杆菌(HP)感染者血清炎性因子水平和HP抗体谱特征。方法 收集2016年12月~2017年12月来院就诊的CHD和健康体检者的血清样本524例,分别设为CHD组(疾病组)296例与非CHD组(对照组)228例,采用血清HP抗体进行检测,筛选CHD并发HP感染患者,另采用化学发光法和免疫印迹法对相应的炎性因子和HP血清抗体谱进行检测,比较两组人群各指标间的差异性。**结果** 在两组人群中疾病组的HP抗体阳性率(52.03%,154/296)高于对照组(35.09%,80/228),差异具有统计学意义($\chi^2=14.95$, $P<0.05$),疾病组各炎性因子含量均高于对照组,两组间差异均具有统计学意义($t=-33.34\sim-19.96$,均 $P<0.05$);疾病组并发HP感染与对照组的抗体谱分析发现,VacA-95KD,VacA-91KD,UreA-66KD和UreB-30KD抗体在两组间的阳性率差异均无统计学意义($\chi^2=0.22\sim3.49$,均 $P>0.05$),而疾病组并发HP感染患者血清CagA-116KD抗体阳性率(76.62%,118/154)高于对照组中HP感染者(62.5%,50/80),且两组间的差异具有统计学意义($\chi^2=5.19$, $P<0.05$),疾病组中并发HP感染者血清I型阳性率(76.62%,118/154)高于对照组并发HP感染者(62.5%,50/80),两组间差异具有统计学意义($\chi^2=5.19$, $P<0.05$)。疾病组按照HP感染血清型间及与非感染患者血清因子间比较发现,I型血清型血清超敏C反应蛋白(hs-CRP)、同型半胱氨酸(Hcy)、肿瘤坏死因子- α (TNF- α)和白细胞介素-6(IL-6)的含量高于II型血清型,且II型血清型hs-CRP,TNF- α ,IL-6和Hcy的含量高于非HP感染CHD患者,各组间差异均具有统计学意义($F=524.8\sim2829.29$,均 $P<0.05$)。**结论** 该文对于CHD患者并发HP感染的血清学特征进行调查,验证了CHD发生于HP感染之间的关联性,积累了HP感染的流行病学资料,为进一步研究CHD的发生、发展以及治疗奠定了科学依据。

关键词:冠心病;幽门螺杆菌;血清幽门螺杆菌抗体;血清抗体谱

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Correlation Analysis of Serum Antibody Spectrum and Inflammatory Factor Level in Patients with Coronary Heart Disease Complicated with *Helicobacter Polori* Infection

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Abstract; Objective To investigate the levels of serum inflammatory factors and the characteristics of HP antibody spectrum in patients with coronary heart disease (CHD) complicated with *Helicobacter pylori* (HP). **Methods** 524 serum samples were collected from CHD patients and health examinees from December 2016 to December 2017, 296 in CHD group and 228 in non-CHD group. Serum HP antibody was used to screen patients with CHD complicated with HP infection. The corresponding inflammatory factors and HP serum antibody spectrum were detected by chemiluminescence and immunoblotting, respectively. The differences of two groups were compared among population indices. **Results** The positive rate of HP antibody in the two groups (52.03%, 154/296) was higher than that in the control group (35.09%, 80/228). The difference was statistically significant ($\chi^2=14.95$, $P<0.05$). The content of inflammatory factors in the disease group was higher than that in the control group, and the difference was statistically significant ($t=-33.34\sim-19.96$, all $P<0.05$). The antibody analysis of patients of HP infection in the disease group and the control group showed no statistically significant difference in the positive rate of VacA-95KD, VacA-91KD, UreA-66KD and UrteB-30KD antibody between the two groups ($\chi^2=0.22\sim3.49$, all $P<0.05$). The positive rates of serum CagA-116KD antibodies in patients with HP infection in the disease group (76.62%, 118/154) were higher than those in the control group (62.5%, 50/80), and the difference between the two groups was statistically significant ($\chi^2=5.19$, $P<0.05$). The positive rates of serum type I antibodies in patients with HP infection in the disease group (76.62%, 118/154) were higher than those in the control group (62.5%, 50/80). The difference between the two groups was statistically significant ($\chi^2=5.19$, $P<0.05$). 118/154 were higher than those in the control group (62.5%, 50/80). There was a significant difference between the two groups ($\chi^2=5.19$, $P<0.05$). According to the com-

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parison between serotypes of HP infection and serum factors of non-HP infected patients, the levels of serum type I hypersensitive C-reactive protein (hs-CRP), homocysteine (Hcy), tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6) were higher than those of type II serotype, and the levels of serum type II Hs-CRP, TNF-alpha, IL-6 and H cysteine were higher than those of non-HP infected CHD patients. The difference was statistically significant ($F=524.8 \sim 2829.29$, all $P < 0.05$). **Conclusion** The serological characteristics of CHD patients complicated with HP infection were investigated in this paper. The correlation between the occurrence of CHD and HP infection was verified. The epidemiological data of HP infection were accumulated, which laid a scientific basis for further research on the occurrence, development and treatment of CHD.

Keywords: coronary heart disease; *Helicobacter pylori*; serum HP antibody; serum antibody spectrum

随着国内经济的高速发展和人们生活物质水平的不断提高,冠心病(coronary heart disease, CHD)在我国的年发病率呈逐年上升的趋势^[1-2],已引起了国内老年病学、心血管病学专家的广泛关注。近年来,有报道显示幽门螺杆菌(*helicobacter pylori*, HP)感染与冠心病的发生、发展存在着密切联系,但有关机制尚不完全清楚,可能与HP感染引起的炎症、免疫反应、吸收功能障碍等因素相关^[3-5]。另外,HP感染与胃肠道疾病发生密切相关^[6-7]。有文献报道HP的细胞毒素相关蛋白(CagA)是引起CHD的重要致病因子之一,其在CHD的发病中起到重要作用^[8-9]。目前,在CHD并发HP感染者中,有关血清HP抗体谱和炎性因子特征的报道较少。因此本文旨在探讨CHD并发HP感染者HP阳性率、炎性因子、血清HP抗体谱以及血清型分布特征,间接说明其与CHD发生的相关性。详细的研究如下。

1 材料与方法

1.1 研究对象 收集2016年12月~2017年12月,西湖区中西医结合医院收治的疑似CHD病人,采用选择性冠状动脉造影,选择左主干、左前降支、左回旋支及右冠状动脉中至少有一支狭窄程度 $\geq 50\%$ 者诊断为CHD^[10],共收集296例CHD患者(疾病组)血清样本,其中男性158例,女性138例,平均年龄 66.5 ± 12.4 岁。另收集同期体检者228例非冠心病血清,其中男性128例,女性100例,平均年龄 65.7 ± 12.6 岁。所有研究对象近期均未出现消化系统疾病、肝肾功能不全及抗HP治疗等。

1.2 试剂和仪器 血清幽门螺杆菌抗体检测试剂盒(杭州艾康生物有限公司),幽门螺杆菌免疫印迹试验(WB)试剂盒(深圳市伯劳特生物制品有限公司),血清超敏C反应蛋白(hs-CRP)和同型半胱氨酸(Hcy)(北京利德曼生化股份有限公司),于雅培C16000全自动生化分析仪上检测。采用西门子公司生产的IMMULITE 1000全自动化学发光仪及其配套试剂测定血清中肿瘤坏死因子- α (TNF- α)和白细胞介素-6(IL-6)。

1.3 方法

1.3.1 标本收集:患者清晨空腹采样,常规无菌采集静脉血,分离血清3ml,-70℃冻存备用。

1.3.2 血清HP抗体及炎性因子检测:采集与分离受检者血清标本,严格按照试剂盒说明书操作和判断结果。血清超敏C反应蛋白(hs-CRP)、同型半胱氨酸(Hcy)、肿瘤坏死因子- α (TNF- α)和白细胞介素-6(IL-6),全部操作严格按照仪器操作规程和试剂说明书执行。

1.3.3 血清抗体谱检测(WB)和血清分型:若研究对象血清HP抗体检测结果为阳性,则进行HP血清抗体谱(WB)分析,严格按照试剂盒说明书进行操作;区带结果有:当尿素酶亚单位(UreA-66KD, UreB-30KD)、空泡毒素(VacA-95KD, VacA-91KD)和细胞毒素相关蛋白(CagA-116KD),并进行分型结果判断:依据说明书进行分型,若CagA, VacA区带抗体中有任一个区带抗体阳性,结果判为血清型I型;三者都阴性而UreA, UreB阳性则为II型。

1.4 统计学分析 HP抗体及其抗体谱中各抗体的阳性率差异采用 χ^2 检验,计数资料用百分率(%)表示,多组间炎性因子水平比较采用方差分析(F检验),两组间的比较采用t检验,计量资料以均数 \pm 标准差($\bar{x} \pm s$)表示,所有数据在SPSS 19.0统计软件包上进行, $P < 0.05$ 为差异具有统计学意义。

2 结果

2.1 疾病组与对照组间HP抗体阳性率及炎性因子比较 见表1。

表1 两组hs-CRP, IL-6, TNF- α 和Hcy含量比较($\bar{x} \pm s$)

项 目	对照组($n=228$)	疾病组($n=296$)	t	P
hs-CRP(mg/L)	1.5 ± 0.9	4.5 ± 1.3	-20.43	<0.001
IL-6(ng/L)	5.9 ± 1.4	13.6 ± 1.8	-33.34	<0.001
TNF- α (ng/L)	12.3 ± 2.4	22.5 ± 2.6	-31.58	<0.001
Hcy($\mu\text{mol}/\text{L}$)	11.9 ± 2.3	17.4 ± 2.5	-19.96	<0.001

对疾病组和对照组进行HP抗体和炎性因子检测可知,在两组人群中疾病组的HP抗体阳性率(52.03%, 154/296)高于对照组(35.09%, 80/

228),两组间差异具有统计学意义($\chi^2 = 14.95$, $P < 0.05$)。疾病组各炎性因子(hs-CRP, IL-6, TNF- α 和 Hcy)含量均高于对照组,两组间差异均具有统计学意义($t = -33.34 \sim 19.96$, 均 $P < 0.05$)。

2.2 疾病组与对照组间 HP 抗体谱、血清型特征分析 见表 2。

表 2 疾病组与对照组间血清抗体谱与血清型差异性比较[n(%)]

项目	对照组 (n=80)	疾病组 (n=154)	χ^2	P
HP 血清抗体谱	CagA-116KD	50(62.5) 118(76.6)	5.19	0.023
	Vaca-95KD	48(60.0) 110(71.4)	2.73	0.077
	Vaca-91KD	50(62.5) 115(74.7)	3.49	0.054
	UreA-66KD	74(92.5) 150(97.4)	3.09	0.079
	UreB-30KD	79(98.8) 153(99.4)	0.22	0.636
血清型	I型(%)	50(62.50) 118(76.62)	5.19	0.023
	II型(%)	30(37.50) 36(23.38)		

经比较对照组与疾病组并发 HP 感染的抗体

表 3 疾病组中不同 HP 感染血清型及非 HP 感染患者的炎性因子含量情况($\bar{x} \pm s$)

项目	疾病组			F	P
	I 血清型(n=118)	II 血清型(n=36)	非 HP 感染(n=148)		
hs-CRP(mg/L)	5.2±0.8	3.6±0.6	2.5±0.5	524.8	<0.001
IL-6(ng/L)	16.7±0.6	14.8±0.5	12.3±0.4	2 829.29	<0.001
TNF- α (ng/L)	26.9±0.9	23.5±0.6	20.1±0.6	2 582.26	<0.001
Hcy(μmol/L)	20.2±1.0	17.4±0.8	14.8±0.6	1 380.9	<0.001

3 讨论 在我国,随着经济稳步发展和人们物质生活水平的提高,CHD 的发病率也在逐年增加,而且发病年龄明显年轻化,青壮年的发病率逐年增加^[1-2],这引起了我国卫生领域专家、学者的广泛关注。最早于 1994 年由 MENDALL 等^[11]首次报道了 HP 感染可能与 CHD 发生、发展存在关联性,由此越来越多的国内外学者对 HP 感染在 CHD 发生、发展中的作用展开了相关研究。慢性 HP 感染是否为 CHD 独立危险因素,目前尚无明确结论,并且其致病机制仍存在争议^[12]。HP 为全球范围内流行的病原菌,HP 具有感染性强的特点,有调查显示在我国正常体检人群 HP 的流行率在 40%~46%,并且随着年龄的增长,HP 感染率也随之升高^[13]。

截至目前医学界有关 HP 感染与 CHD 发生、发展的可能性机制推测有^[12,14-15]:①炎性反应:HP 感染可激活炎症细胞分泌 TNF- α , IL-6 在内的细胞因子,引起局部炎症、内皮细胞损伤或功能障碍,导致平滑肌细胞增殖。②HP 感染可引起脂代谢紊乱,促进动脉粥样斑块形成。③营养吸收障碍:

谱分析:VacA-95KD, VacA-91KD, UreA-66KD 和 UreB-30KD 抗体,在两组间的差异无统计学意义($\chi^2 = 0.22 \sim 3.49$, 均 $P > 0.05$),而疾病组并发 HP 感染患者血清 CagA-116KD 抗体阳性率(76.62%, 118/154)高于对照组中 HP 感染者(62.5%, 50/80),且两组间的差异具有统计学意义($\chi^2 = 5.19$, $P < 0.05$),疾病组中并发 HP 感染者血清 I 型阳性率(76.62%, 118/154)高于对照组并发 HP 感染者(62.5%, 50/80),两组间差异具有统计学意义($\chi^2 = 5.19$, $P < 0.05$)。

2.3 疾病组中不同 HP 感染血清型及非 HP 感染患者的炎性因子水平调查 见表 3。疾病组按照 HP 感染血清型间及与非感染患者血清因子间比较,I 型血清型 hs-CRP, TNF- α , IL-6 和 Hcy 的含量高于 II 型血清型,且 II 型血清型 hs-CRP, TNF- α , IL-6 和 Hcy 的含量高于非 HP 愄染患者,各组间差异具有统计学意义(均 $P < 0.05$)。

HP 感染可引起胃肠功能异常,致使维生素 B12, B6 和叶酸吸收不良,进而引起维生素 B12, B6 和叶酸缺乏,导致 Hcy 水平升高,加剧 CHD 的发生。④免疫反应:CagA 抗体与内皮细胞表面抗原、平滑肌细胞发生交叉反应,促使动脉粥样硬化的发生。以上机制看似相互独立,但彼此之间却存在着内在的密切联系,本研究就其部分机制间的关联性进行了研究。

本文结果显示在 CHD 患者中 HP 感染的阳性率要高于非 CHD 组(见表 1),差异具有统计学意义($P < 0.05$),与国内外文献报道一致,间接提示 HP 感染与 CHD 的发生发展存在关联性。另外本文比较了 CHD 组与非 CHD 组炎性因子(hs-CRP, TNF- α , IL-6 和 Hcy)的含量,发现 CHD 组炎性因子 hs-CRP, TNF- α , IL-6 和 Hcy 的含量要高于对照组,同样证实了文献报道的 hs-CRP, TNF- α , IL-6 和 Hcy 这些因子与 CHD 的发生、发展存在着直接联系。然而,各炎性因子与 HP 感染及不同血清型别间是否存在联系? 我们对疾病组与对照组间并发 HP 感染的血清型别和抗体谱进

行调查发现(见表2),疾病组中并发HP感染的患者血清型以I型为主(CagA抗体为主要分型依据),且阳性率高于对照组,两组间的差异存在统计学意义($P<0.05$),说明了HP感染CagA抗体阳性或血清型I型较HP感染CagA抗体阴性或血清型II型,对CHD的发生、发展起到了关键作用。另外我们将疾病组依据HP感染的血清型别及是否HP感染进行再分组(血清型I,血清型II,非HP感染)(见表3),发现这三个亚组中,I型血清型hs-CRP,TNF- α ,IL-6和Hcy的含量高于II型血清型,II型血清型hs-CRP,TNF- α ,IL-6和Hcy的含量高于非HP感染CHD患者,各组间差异具有统计学意义($P<0.05$),进一步说明了HP感染引起CHD发生的各机制间相互交织在一起,HP感染血清型I型(CagA抗体阳性)较血清型II型可能会更大程度的引起血管发生免疫反应,同时严重的免疫反应又加剧了炎性反应的发生,但详细的发生过程有待于进一步的研究证实。

综上所述,HP感染作为CHD发生的一个重要因素,其机制尚不完全清楚,本文研究积累了CHD并发HP感染的流行病学资料以及血清特征性抗体谱资料,发现了CHD并发HP感染患者中各致病机制间存在着内在的关联性,为进一步研究CHD的发生、发展以及治疗奠定了科学依据。

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