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HBV-DNA载量水平与血清学标志物分组模式 及前S1抗原的关系

沙启明

(六安市中医院检验科, 安徽 六安 237000)

[摘要] 目的: 探讨乙型肝炎病毒DNA(hepatitis B virus DNA, HBV-DNA)载量水平与血清学标志物(hepatitis B virus markers, HBVM)分组模式以及前S1抗原(Pre-S1 antigen, Pre-S1Ag)的关系。方法: 收集2018年6月至2020年7月来院就诊的180例慢性乙肝患者的血清样本, 采用实时荧光定量聚合酶链反应(qRT-PCR)技术检测血清HBV-DNA载量水平; 采用化学发光免疫分析法(CLIA)检测乙肝表面抗原(HBsAg)、e抗原(HBeAg)、表面抗体(抗HBs)、e抗体(抗HBe)、核心抗体(抗HBc), 并归纳受检样本的HBVM分组模式; 采用ELISA法检测血清Pre-S1Ag。分析HBV-DNA载量水平、HBVM分组模式和Pre-S1Ag水平的关系。结果: 180例血清样本, HBsAg⁺/抗HBe⁺/抗HBc⁺模式85例(47.22%), HBsAg⁺/HBeAg⁺/抗HBc⁺模式70例(38.89%), 其他模式25例(13.89%)。HBsAg⁺/HBeAg⁺/抗HBc⁺模式组HBV-DNA、Pre-S1Ag阳性率均明显高于HBsAg⁺/抗HBe⁺/抗HBc⁺模式组及其他模式组, 差异有统计学意义($\chi^2=56.955$ 、 46.809 , $P<0.05$)。将HBV-DNA阳性作为判断HBV复制的金标准, HBeAg的灵敏度为87.23%, 特异度为65.12%, 阳性预测值为73.21%, 阴性预测值为82.35%; Pre-S1Ag的灵敏度为90.35%, 特异度为86.36%, 阳性预测值为91.96%, 阴性预测值为83.82%。依据HBV-DNA载量检测水平, 分成 $<10^3$ copies/mL、 $10^3\sim 10^5$ copies/mL、 $10^5\sim 10^7$ copies/mL、 $>10^7$ copies/mL的4个亚组。随着HBV-DNA载量水平升高, Pre-S1Ag阳性率逐渐升高, 分别为41.18%、64.00%、77.78%、94.29%, 差异具有统计学意义($\chi^2=31.250$, $P<0.05$)。结论: HBV血清学标志物和Pre-S1Ag均可用于辅助诊断是否感染HBV以及HBV复制水平, 但尚不可取代HBV-DNA定量检测, 三者联合检测能为临床诊断、病毒复制提供更全面的依据。

[关键词] 乙型肝炎病毒载量; 荧光定量聚合酶链反应技术; 血清学标志物模式; 化学发光免疫分析法; 前S1抗原; ELISA法

Relationship between HBV-DNA load levels and grouping mode of serological markers and Pre-S1 antigen

SHA Qiming

(Department of Clinical Laboratory, Traditional Chinese Medicine Hospital of Lu'an, Lu'an Anhui 237000, China)

Abstract **Objective:** To explore the relationship between hepatitis B virus (HBV) DNA (HBV-DNA) load levels and

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通信作者 (Corresponding author): 沙启明, Email: 523574137@qq.com

grouping mode of serological markers of hepatitis B (HBVM) and Pre-S1 antigen (Pre-S1Ag). **Methods:** Serum samples were collected from 180 patients with chronic hepatitis B who came to the hospital for treatment between June 2018 and July 2020. Serum HBV-DNA load levels were detected by quantitative real-time polymerase chain reaction (qRT-PCR). Hepatitis B surface antigen (HBsAg), hepatitis e antigen (HBeAg), surface antibody (anti-HBs), e antibody (anti-HBe) and core antibody (anti-HBc) were detected by chemiluminescence immunoassay (CLIA), and the HBVM grouping mode of the samples was summarized. Serum Pre-S1Ag was detected by enzyme linked immunosorbent assay (ELISA). The relationship between HBV-DNA load levels, HBVM grouping mode and Pre-S1Ag level was analyzed. **Results:** Among the 180 serum samples, there were 85 cases (47.22%) of HBsAg⁺/anti-HBe⁺/anti-HBc⁺ mode, 70 cases (38.89%) of HBsAg⁺/HBeAg⁺/anti-HBc⁺ mode and 25 cases (13.89%) of other modes. The positive rates of HBV-DNA and Pre-S1Ag in HBsAg⁺/HBeAg⁺/anti-HBc⁺ mode group were significantly higher than those in HBsAg⁺/anti-HBe⁺/anti-HBc⁺ mode group and other mode group ($\chi^2=56.955, 46.809, P<0.05$). The sensitivity, specificity, positive predictive value and negative predictive value of HBeAg were 87.23%, 65.12%, 73.21% and 82.35% respectively when positive HBV-DNA was used as the gold standard for judging HBV replication. The sensitivity, specificity, positive predictive value and negative predictive value of Pre-S1Ag were 90.35%, 86.36%, 91.96% and 83.82% respectively. According to the HBV-DNA load detection levels, the patients were divided into four subgroups, including $<10^3$ copies/mL, 10^3-10^5 copies/mL, 10^5-10^7 copies/mL and $>10^7$ copies/mL subgroups. With the increase of HBV-DNA load levels, the positive rate of Pre-S1Ag was gradually increased, which were 41.18%, 64.00%, 77.78% and 94.29% respectively, with a statistically significant difference ($\chi^2=31.250, P<0.05$). **Conclusion:** Both serological markers of HBV and Pre-S1Ag can be used to assist in the diagnosis of HBV infection and HBV replication levels, but they cannot replace HBV-DNA quantitative detection, and the combined detection of the three indicators can provide a more comprehensive basis for clinical diagnosis and viral replication.

Keywords hepatitis B virus load; quantitative real-time polymerase chain reaction; serological marker mode; chemiluminescence immunoassay; Pre-S1 antigen; enzyme linked immunosorbent assay

乙型肝炎病毒(hepatitis B virus, HBV)包含的正嗜肝DNA病毒属易引起乙型肝炎, 普通人群均易感, 其中5%~10%乙型肝炎患者可进展为肝硬化、肝癌, 不仅增加治疗难度, 而且预后较差^[1]。因此早期诊断并评估病情, 对临床疾病预防、病情控制和指导抗病毒治疗等尤为重要。乙肝两对半是目前判断HBV感染的常规检测项目, 乙肝表面抗原(HBV surface antigen, HBsAg)阳性是HBV的标志, e抗原(HBeAg)阳性表示HBV复制活跃。但乙肝两对半检测存在“窗口期”和“病毒免疫逃避”等不足, 易造成假阴性, 也不能反映体内HBV载量水平和传染性等重要信息。HBV载量检测直观反映体内HBV复制情况, 为HBV感染诊断、传染性和疗效评估提供可靠指标^[2], 近些年国内已加强HBV载量检测项目的推广, 但仍有一部分地区尤其是中基层医院尚未开展。前S1抗原(Pre-S1 antigen, Pre-S1Ag)是HBV外膜蛋白的重要成分, 出现在HBV感染的最早期, 参与HBV感

染、病毒复制和机体免疫反应的全过程, 早期诊断HBV感染的敏感性较好^[3]。本文探讨HBV载量水平、血清学标志物(serological markers of hepatitis B, HBVM)模式和Pre-S1Ag的相互关系, 为临床完善诊疗及病情评估寻找依据。

1 对象与方法

1.1 对象

研究对象为2018年6月至2020年7月来院就诊的180例慢性乙肝患者, 其中男109例(60.56%), 女71例(39.44%), 年龄18~77(45.70±6.31)岁。纳入标准: 1)诊断标准符合《慢性乙型肝炎防治指南》^[4]; 2)年龄不超过80岁, 对研究知情同意。排除标准: 1)影像学检查明确肝脏恶性肿瘤; 2)合并严重器质性病变、精神性疾病或正接受放化疗者; 3)近6个月接受过乙型肝炎抗病毒治疗。本研究经六安市中医院医学伦理委员会审查批准。

1.2 方法

采集空腹静脉血 5 mL, 离心提取血清, -20 °C 冰箱冷存, 以备检测。检测血清谷草转氨酶(aspartate aminotransferase, AST)、谷丙转氨酶(alanine aminotransferase, ALT)等常规肝功能指标, AST正常范围水平4.0~40.0 U/L, ALT正常范围水平0~40 U/L。同时进行下列检测。

1.2.1 HBV-DNA 载量检测

采用实时荧光定量聚合酶链反应(quantitative real-time polymerase chain reaction, qRT-PCR)检测, 仪器为美国ABI 7200荧光定量PCR仪, 试剂盒购自于艾康生物科技有限公司(批号202005036), HBV-DNA载量水平 $<10^3$ copies/mL表示阴性。

1.2.2 HBVM 检测及模式分组

采用化学发光免疫分析法(Chemiluminescence immunoassay, CLIA)检测HBsAg、HBeAg、表面抗体(anti-HBs, 抗HBs)、e抗体(anti-HBe, 抗HBe)、核心抗体(anti-HBc, 抗HBc), 检测仪器为雅培I2000, 试剂盒购自于雅培(上海)贸易有限公司(批号: 14128F N01)。

1.2.3 血清 Pre-S1Ag 检测

采用ELISA法进行检测, 试剂盒购自英科新创(厦门)有限公司(批号2020097708N), 严格按说明书操作, 反应孔引物浓度: 阴性对照 $\geq 2:1$ 为阳性。

1.3 统计学处理

采用SPSS 20.0统计学软件分析数据, 计量资料经检验均满足正态分布, 用均数 \pm 标准差($\bar{x}\pm s$)描述, 多组间比较采用单因素方差(ANOVA)检验, 两两比较采用t检验; 计数资料用百分比描述, 组

间差异比较采用卡方检验, 等级资料采用Kruskal-Wallis秩和检验。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 HBVM 模式检出情况

180例血清样本共检出9种HBVM模式, 其中HBsAg⁺/抗HBe⁺/抗HBc⁺模式组85例, 占47.22%; HBsAg⁺/HBeAg⁺/抗HBc⁺模式组70例, 占38.89%; 其他HBVM模式包括HBsAg⁺/HBeAg⁺/抗HBe⁺/抗HBc⁺、HBsAg⁺/抗HBs⁺/抗HBe⁺/抗HBc⁺、HBsAg⁺/HBeAg⁺/抗HBs⁺/抗HBc⁺、HBsAg⁺/HBeAg⁺/抗HBs⁺/抗HBe⁺/抗HBc⁺、HBsAg⁺/抗HBs⁺/抗HBe⁺/抗HBc⁺、HBsAg⁺/抗HBc⁺、抗HBe⁺、因例数较少, 故分组时进行合并, 共25例, 占13.89%。

2.2 不同 HBVM 模式的 HBV-DNA、Pre-S1Ag 阳性率分析

HBsAg⁺/HBeAg⁺/抗HBc⁺模式组HBV-DNA、Pre-S1Ag阳性率均明显高于HBsAg⁺/抗HBe⁺/抗HBc⁺模式组及其他模式组, 差异有统计学意义($\chi^2=56.955$ 、46.809, $P<0.05$; 表1)。

2.3 HBV-DNA 检出率与 HBeAg、Pre-S1Ag 的关系

将HBV-DNA阳性作为判断HBV复制的金标准, 评价HBeAg、Pre-S1Ag。HBeAg的灵敏度为87.23%, 特异度为65.12%, 阳性预测值为73.21%, 阴性预测值为82.35%; Pre-S1Ag的灵敏度为90.35%, 特异度为86.36%, 阳性预测值为91.96%, 阴性预测值为83.82%(表2)。

表1 不同HBVM模式的HBV-DNA、Pre-S1Ag阳性率比较

Table 1 Comparison of positive rates of HBV-DNA and Pre-S1Ag in different HBVM modes

HBVM模式	n	HBV-DNA/[例(%)]		Pre-S1Ag/[例(%)]	
		阳性	阴性	阳性	阴性
HBsAg ⁺ /HBeAg ⁺ /抗HBc ⁺ 模式组	70	67 (95.71)	3 (4.29)	65 (92.86)	5 (7.14)
HBsAg ⁺ /抗HBe ⁺ /抗HBc ⁺ 模式组	85	38 (44.71) [*]	47 (55.29)	42 (49.41) [*]	43 (50.59)
其他模式组	25	7 (28.00) [*]	18 (72.00)	7 (28.00) [*]	18 (72.00)
合计	180	112 (62.22)	68 (37.78)	114 (63.33)	66 (36.67)

与HBsAg⁺/HBeAg⁺/抗HBc⁺模式组比较, ^{*} $P<0.05$ 。

Compared with HBsAg⁺/HBeAg⁺/anti-HBc⁺ mode group, ^{*} $P<0.05$.

表2 HBV-DNA检出率与HBeAg、Pre-S1Ag的关系

Table 2 Relationship between HBV-DNA detection rate and HBeAg and Pre-S1Ag

HBV-DNA	n	HBeAg/[例(%)]		Pre-S1Ag/[例(%)]	
		阳性	阴性	阳性	阴性
阳性	112	82 (73.21)	30 (26.79)	103 (91.96)	9 (8.04)
阴性	68	12 (17.65)	56 (82.35)	11 (16.18)	57 (83.82)
合计	180	94 (35.56)	86 (91.49)	114 (63.33)	66 (36.67)

2.4 HBV-DNA 载量水平与 Pre-S1Ag 的关系

依据HBV-DNA载量检测水平, 分成 $<10^3$ copies/mL、 $10^3\sim 10^5$ copies/mL、 $10^5\sim 10^7$ copies/mL、 $>10^7$ copies/mL的4个亚组。随着HBV-DNA载量水平升高, Pre-S1Ag阳性率逐渐升高, 分别为41.18%、64.00%、77.78%、94.29%, 差异具有统计学意义($\chi^2=31.250$, $P<0.05$; 表3)。

2.5 不同 HBV-DNA 载量水平的 AST、ALT 水平比较

随HBV-DNA载量水平升高, AST、ALT水平也随之逐渐升高。不同HBV-DNA载量组间AST、ALT水平比较, 差异有统计学意义($t_1=8.059$ 、 4.257 、 2.695 , $t_2=5.075$ 、 5.073 、 3.416 , $P<0.05$; 表4)。

表3 HBV-DNA载量与血清Pre-S1Ag阳性率分析

Table 3 Analysis of HBV-DNA load and serum Pre-S1Ag positive rates

HBV-DNA载量	Pre-S1Ag/[例(%)]	
	阳性(n=114)	阴性(n=66)
$<10^3$ copies/mL	28 (41.18)	40 (58.82)
$10^3\sim 10^5$ copies/mL	32 (64.00)	18 (36.00)
$10^5\sim 10^7$ copies/mL	21 (77.78)	6 (22.22)
$>10^7$ copies/mL	33 (94.29) [#]	2 (5.71)

与其他HBV-DNA载量水平亚组比较, $*P<0.05$ 。

Compared with other HBV-DNA load subgroups, $*P<0.05$.

表4 不同HBV-DNA载量水平的AST、ALT水平比较

Table 4 Comparison of AST and ALT levels at different HBV-DNA load levels

HBV-DNA载量	n	肝功能指标	
		AST/(U·L ⁻¹)	ALT/(U·L ⁻¹)
$<10^3$ copies/mL	68	31.59 ± 8.30	42.08 ± 10.35
$10^3\sim 10^5$ copies/mL	50	49.70 ± 15.82*	60.28 ± 27.03*
$10^5\sim 10^7$ copies/mL	27	67.50 ± 20.31*	92.73 ± 26.32*
$>10^7$ copies/mL	35	83.08 ± 24.16*	118.20 ± 31.07*

与HBV-DNA阴性者比较, $*P<0.05$ 。

Compared with HBV-DNA negative, $*P<0.05$.

3 讨论

近些年随着HBV预防疫苗推广和居民防护意识提高,我国HBV感染率有明显下降^[5],但考虑到我国HBV感染人群的基数庞大,肝硬化、肝癌者治疗困难,不同地区、级别医疗机构的检测水平参差不齐,因此加强HBV早期诊断和病情评估,仍具有临床意义和社会意义。本研究180例乙型肝炎血清样本CLIA共检出9种HBVM模式,鉴于乙型肝炎的临床特点复杂性,同时检测HBV-DNA载量水平和Pre-S1Ag阳性率,并进行综合分析。

本研究结果显示:在不同HBVM模式下HBV-DNA的阳性率存在差异,HBsAg⁺/HBeAg⁺/抗HBe⁺模式组HBV-DNA阳性率高达95.71%,而HBsAg⁺/抗HBe⁺/抗HBe⁺模式组和合并模式组仅为44.71%、28.00%,表明HBeAg和HBV-DNA存在紧密关联,HBeAg阳性是HBV复制活跃的重要标志,HBeAg转阴通常被认为HBV复制活跃度减弱,传染性下降。但临床发现,部分乙型肝炎患者经抗病毒治疗后HBeAg转阴,但疲乏劳累、面色萎黄等症状仍未改善,甚至加剧,AST、ALT水平持续异常,肝功能损害程度加深。本研究也发现26.79%HBV-DNA阳性者的HBeAg检测呈阴性,即HBeAg阴性者仍可能存在HBV活跃复制^[6]。有报道^[7-8]分析:HBeAg阴性乙型肝炎患者存在HBV DNA前C区、基本核心启动子(basic core promoter, BCP)区的基因变异,抑制了HBeAg表达,但不影响HBV复制。加上近些年抗病毒药物的广泛使用,可能加剧了HBV-DNA前C区和BCP区的基因变异。因此确定HBVM模式后,进行HBV-DNA载量水平检测尤为重要,HBV-DNA阳性作为HBV复制的金标准,对HBeAg阴性但HBV-DNA阳性者需引起重视,避免假阴性。

本研究选择Pre-S1Ag进行检测,原因在于人体HBV感染早期,Pre-S1Ag最早引起机体免疫应答,可作为HBV病毒复制和传染性评估的有效指标,与HbsAg阳性但Pre-S1Ag阴性者比较,HbsAg、Pre-S1Ag均为阳性者的危险性更大,若HbsAg阴性但Pre-S1Ag阳性,考虑为隐性HBV感染者。因此Pre-S1Ag和常规两对半检测可相互补充^[9-10]。本研究结果显示:随着HBV-DNA载量水平升高,Pre-S1Ag阳性率也逐渐升高,HBV-DNA阳性者的Pre-S1Ag阳性率达91.96%,Pre-S1Ag与HBV-DNA在评估病毒复制方面一致性较好。Pre-S1Ag筛查HBV的灵敏度和特异度(90.35%、86.36%)均高于HBeAg,表明Pre-S1Ag检测对病毒复制的诊断敏感性优于

HBeAg^[11]。针对HBeAg阴性的乙型肝炎患者,若缺乏HBV-DNA检测条件,可进行Pre-S1Ag检测,能降低HBV-DNA前C区和BCP区基因变异所致的漏诊风险,使临床诊断和疗效评估更精确。

乙型肝炎患者HBV-DNA载量水平和肝功能的的关系值得研究,AST、ALT均是反映肝功能的敏感指标。已有研究^[12-13]发现:HBV-DNA载量水平与AST、ALT呈正相关($r=0.4579$ 、 0.4036)。但部分HBV-DNA载量水平急剧升高者AST、ALT的变化并不明显,肝功能损害并未加重。本研究结果显示:随着HBV-DNA载量水平升高,AST、ALT水平也随之升高,与上述研究存在吻合,提示HBV-DNA载量越高,肝细胞损伤程度越严重,需及时进行抗病毒治疗,减轻肝功能损害。但考虑到肝损伤的影响因素复杂,除HBV-DNA载量水平外,合并遗传代谢性疾病、酒精、肥胖、药物等因素均可导致肝损伤^[14],且HBV-DNA载量水平与肝细胞炎症和组织纤维化程度的关系不明确^[15-16],因此HBV-DNA载量水平可作为评估肝功能损害程度的参考指标,但不是准确指标,需多次检测HBV-DNA载量水平、结合临床症状体征和肝功能异常史等进行评估,有条件时进行肝穿刺活检进一步明确,对预防和指导肝硬化治疗,改善预后具有重要意义。有学者^[17]对此类高HBV-DNA病毒载量水平、ALT水平正常的HBV感染者进行分析,发现相当比重患者已发生肝脏组织学改变,且 ≥ 50 岁人群最为明显,年龄是预测肝脏坏死炎症和纤维化的独立预测因子,建议行肝活检。

综上,乙型肝炎的临床特点复杂,临床诊疗需引起重视。HBV-DNA载量水平、HBVM模式和Pre-S1Ag联合检测能为临床诊断、病毒复制和肝功能评估以及制订治疗复查计划提供更全面依据。对于尚不具备HBV-DNA检测的地区或医疗单位,可加强Pre-S1Ag检测作为补充依据。本研究存在样本量较少的不足,仍需进行大样本、多中心研究,以进一步为诊断乙型肝炎提供科学准确的临床依据。

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