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乙肝患者血清标志物与肝纤维化血清学指标的相关性分析 *

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摘要 目的:探讨乙肝患者血清标志物与肝纤维化血清学指标的相关性。**方法:**收集我院收治的 136 例乙型病毒肝炎患者,根据轻中重程度分为轻度组、中度组以及重度组,每组 42 例。观察并比较所有患者乙肝血清标志物、HBV-DNA 水平、透明质酸(HA),血清Ⅲ型前胶原肽(PCIII),Ⅳ型胶原(CIV)水平以及层粘连蛋白(LN)水平。**结果:**三组患者的 HBV-DNA 水平依次升高,与轻度组相比,中度组、重度组患者 HBV-DNA 水平较高,与中度组患者相比,重度组患者 HBV-DNA 水平较高,差异具有统计学意义(P<0.05)。与轻度组相比,中度组、重度组患者 HA、PCIII、CIV、LN 水平较高,与中度组患者相比,重度组患者 HA、PCIII 水平较高,差异具有统计学意义(P<0.05);HBV-DNA 水平与 HA、PCIII、CIV、LN 水平均呈显著正相关。**结论:**乙肝患者的血清学检测指标与血清肝纤维化测定有助于对乙肝的纤维化过程的进展情况进行评估。

关键词:乙肝;肝纤维化;乙肝病毒核酸含量

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Correlative Analysis of the Hepatitis B Serological Biomarkers with Serum Liver Fibrosis Biomarkers*

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ABSTRACT Objective: To investigate the significance of serum liver fibrosis in patients with hepatitis B in clinical research. **Methods:** 136 cases of hepatitis B patients admitted to our hospital were divided into 3 groups according to the degree of mild, moderate, severe, mild group, moderate group and severe group, 42 cases in each group. All patients were observed and compared with HBV markers, HBV-DNA levels, hyaluronic acid (HA), serum type III collagen peptide (PCIII), type IV collagen (CIV) and laminin (LN) levels. **Results:** HBV-DNA levels in three groups of patients was gradually increased, compared with that of the mild group, moderate group and severe group and the HBV-DNA level are higher, and compared with moderate group patients, severe group patients HBV-DNA level is higher, the difference is statistically significant (P<0.05). Compared with the mild group, moderate group and severe group patients HA, PCIII, civ and LN levels are higher, and compared with moderate group patients, patients in the severe group ha, PCIII level is higher, the difference is statistically significant (P<0.05); HBV-DNA level was positively correlated with the HA, PCIII, CIV and LN levels. **Conclusions:** The serological detection indexes of hepatitis B patients and serum liver fibrosis were determined, which could be used to evaluate the progress of hepatitis B fibrosis process.

Key words: Hepatitis B; Liver fibrosis; Hepatitis B virus nucleic acid content

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前言

慢性乙型肝炎是常见的慢性传染性疾病之一,乙型肝炎在其迁延发展的过程中，由于患者免疫功能以及耐受力变差,乙肝病毒无法被及时的清除,导致肝脏长期受累,肝细胞外基质发生增生以及沉积,出现结节以及纤维组织增生[1]。肝细胞的坏死可以引起肝纤维化的发生,肝纤维化是肝细胞损伤后机体的修复机制,可能导致肝硬化的发生[2]。据统计,轻、中度肝炎患者发生肝纤维化的几率为 64%,而在重度肝炎患者中其发生率为 100%[3]。目前临床主要以肝组织的病理学检查对肝纤维化程度进行诊断,但存在局限性[4]。近年来,对于血清学指标的研究有了一定的进展。血清透明质酸(HA),血清Ⅲ型前胶原肽(PCIII),Ⅳ型胶原(CIV)水平以及层粘连蛋白(LN)是目前临床应用较多的肝纤维化血清学指标[5]。但乙肝的血清学标志物与肝纤维化血清学指标、肝纤维化的程度间的相关性并不清楚。因此,本研究以慢性乙肝患者为研究对象，通过检测其乙肝血清标志物、乙肝病毒核酸含量以及肝纤维化血清学指标，探讨其相互联系,现将结果报道如下。

1 资料与方法

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1.1 临床资料

收集 2013 年 3 月 ~2016 年 3 月于我院就诊的 136 例慢性乙型肝炎患者，根据轻、中、重程度分为 3 组，分别为轻度组、中度组以及重度组，每组 42 例。轻度组患者平均年龄 (35.54± 1.01)，男性 26 例，女性 16 例；中度组患者平均年龄(35.44± 0.85)岁，男性 24 例，女性 18 例；重度组患者平均年龄(34.85± 0.81)岁，男性 25 例，女性 17 例。所有患者符合乙型病毒肝炎的诊断标准，乙肝病毒感染超过 6 个月；年龄 18~60 岁，性别不限，无心脑血管疾病以及其他重要脏器的重大疾病，无恶性肿瘤，无其他肝病，签署知情同意书同意进行实验。三组患者的一般临床资料相比均无统计学差异，具有可比性(P>0.05)。

1.2 方法

1.2.1 患者乙肝血清标志物、HBV-DNA 水平检测 所有患者采集外周静脉血 3ml，采用 ELISA 法对患者乙肝血清标志物以及 HBV-DNA 水平进行检测。

1.2.2 患者透明质酸(HA)，血清Ⅲ型前胶原肽(PCIII)，Ⅳ型胶原(CIV)水平以及层粘连蛋白(LN)水平检测 所有患者采集外周静脉血 3 mL，采用放射免疫法检测患者 HA、PCIII、CIV、LN 水平。

1.3 统计学分析

采用 SPSS 19.0 统计软件进行分析。计量数据采用 t 检验，以均数± 标准差($\bar{x}$± s)表示；计数资料采用卡方检验，以%表示，相关性采用 Spearman 等级相关分析。以 P<0.05 认为差异有统计学意义。

2 结果

2.1 三组患者乙肝血清标志物、HBV-DNA 水平的比较

轻度组、中度组、中度组三组患者的 HBV-DNA 水平依次升高。与轻度组相比，中度组、重度组患者 HBV-DNA 水平较高(P<0.05)。与中度组患者相比，重度组患者 HBV-DNA 水平较高(P<0.05)。具体见表 1。

表 1 三患者乙肝血清标志物、HBV-DNA 水平的比较($\bar{x}$± s)

Table 1 Comparison of the hepatitis B serum markers and HBV-DNA levels between three groups($\bar{x}$± s)

	n	Hepatitis B serum marker	HBV-DNA(x103)
Mild group	42	Hbs Ag(+)、HBe Ag(+)、HBsAb(-)、HBeAb(+)、HBcAb(+)	1.15± 0.25
Moderate group	42	Hbs Ag(+)、HBe Ag(-)、HBsAb(+)、HBeAb(-)、HBcAb (+)	1.69± 0.33*
Severe group	42	Hbs Ag(+)、HBe Ag(+)、HBsAb(-)、HBeAb (+)、HBcAb(+)	2.78± 0.42*#

注：与轻度组相比，*P<0.05，与中度组相比，#P<0.05.

Note :Compared with Mild group, *P<0.05; Compared with the Moderate group, #P<0.05.

2.2 三组患者 HA、PAIII 水平比较

轻度组、中度组、中度组三组患者的血清 HA、PCIII 水平依次升高。与轻度组相比，中度组、重度组患者 HA、PCIII 水平较高(P<0.05)。与中度组患者相比，重度组患者 HA、PCIII 水平较高(P<0.05)。具体见表 2。

表 2 三组患者 HA、PAIII 水平比较($\bar{x}$± s)

Table 2 Comparison of the HA, PAIII levels between three groups($\bar{x}$± s)

	n	HA(ng/mL)	PCIII(μg/L)
Mild group	42	204.38± 58.01	124.02± 15.82
Moderate group	42	315.23± 66.28*	158.28± 15.45*
Severe group	42	411.63± 49.94*#	196.73± 16.27*#

注：与轻度组相比，*P<0.05，与中度组相比，#P<0.05.

Note: Compared with Mild group, *P<0.05; Compared with the Moderate group, #P<0.05.

2.3 三组患者 LN、CIV 水平比较

轻度组、中度组、中度组三组患者的血清 LN、CIV 水平依次升高。与轻度组相比，中度组、重度组患者 LN、CIV 水平较高(P<0.05)。与中度组患者相比，重度组患者 LN、CIV 水平较高(P<0.05)。具体见表 3。

表 3 三组患者 LN、CIV 水平的比较(μg/L, $\bar{x}$± s)

Table 3 Comparison of the LN, CIV levels between three groups (μg/L, $\bar{x}$± s)

	n	LN	CIV
Mild group	42	151.33± 34.19	79.92± 21.01
Moderate group	42	199.28± 22.84*	135.29± 14.04*
Severe group	42	223.83± 26.01*#	188.24± 21.82*#

注：与轻度组相比，*P<0.05，与中度组相比，#P<0.05.

Note: Compared with Mild group, *P<0.05; Compared with the Moderate group, #P<0.05.

2.4 HBV-DNA 与 IV-C、PCIII、LN 及 HA 的相关性分析

HBV-DNA 水平与透明质酸(HA)、血清Ⅲ型前胶原肽(PCI-

II)、Ⅳ型胶原(CIV)水平以及层粘连蛋白(LN)水平均呈正相关，相关系数 r 值分别为 0.514、0.437、0.442、0.471，P 值均＜0.01。

3 讨论

慢性病毒性肝炎是机体免疫功能失调，致病因素的持续作用，导致其重要病理特点为胶原蛋白等等细胞外基质在肝内沉积导致肝细胞纤维组织增生，最终导致肝纤维化[6]。肝纤维化是由于不同病因造成的慢性肝损伤的共有反应[7]。有研究证实[8]肝纤维化的病理过程可逆，早期的及时治疗能够阻断肝纤维化的病理进展。以往临床通常肝组织的病理检查作为诊断肝纤维化[9]。但肝组织活检为创伤性检查，且具有一定的局限性，因此难以进行跟踪和随访[10]。本实验结果显示血清透明质酸(HA)、血清Ⅲ型前胶原肽(PCIII)、Ⅳ型胶原(CIV)水平以及层粘连蛋白(LN) 四项肝纤维化指标在不同程度的乙型肝炎患者血清中的水平不同，随着肝损害的程度的加重而升高。

血清透明质酸(HA)合成于肝间质成纤维细胞，在内皮细胞中被摄取和降解。在生理状态下，人体内存在着透明质酸的清除剂，透明质酸水平极低[11]。肝脏成纤维细胞或者内皮细胞的受损都将导致血清透明质酸水平失常，乙肝病毒患者存在着成纤维细胞的增加和内皮细胞摄取血清透明质酸功能的降低，血清血清透明质酸水平升高，且已有研究证实[12-14]肝炎的活动越明显，血清透明质酸的水平越高，表明 HA 是判断肝纤维化程度的重要指标[15]。本实验结果显示中度组、重度组患者 HA 水平较高，与中度组患者相比，重度组患 HA 水平较高，血清透明质酸与 HBA-DNA 水平呈正相关。

同Ⅳ型胶原(CIV)主要存在于汇管小血管周围，在细胞黏附以及基因表达中发挥重要作用，是基底膜的成分之一[16]。当肝纤维化发生时，肝基底膜胶原发生变化，同Ⅳ型胶原水平增加，且已有研究结果显示同Ⅳ型胶原水平的升高与肝组织纤维化水平呈正相关[17]。层粘连蛋白(LN)合成于内皮细胞以及贮脂细胞中，同Ⅳ型胶原(CIV)相同，也是基底膜的主要成分，是基底膜主要的大分子糖蛋[18]。有研究显示层粘连蛋白(LN)以及Ⅳ型胶原(CIV)水平的升高与肝纤维化以及炎症水平具有密切的联系，是检测肝纤维化的可靠指标之一[19]。本研究结果显示轻度组、中度组、中度组三组患者的血清 LN、CIV 水平依次升高，差异具有统计学意义，提示 LN、CIV 水平的检测能够评估乙肝的纤维化过程的进展情况。

Ⅲ型前胶原肽(PCIII)是Ⅲ型前胶原被蛋白酶切下的 N 端肽。既往已有研究证实血清Ⅲ型前胶原肽水平的升高可以表明肝脏合成Ⅲ型胶原的速率增加，其与肝纤维化形成密切相关[20]。本实验结果显示轻度组、中度组、重度组患者 PCIII 水平依次升高，差异具有统计学意义，PCIII 水平与 HBA-DNA 水平呈正相关。血清Ⅲ型前胶原肽也是反映肝纤维化的指标之一，其水平的升高与炎症、坏死以及肝纤维化有关。

综上所述，对乙肝患者的血清学检测指标与血清肝纤维化进行测定有助于对乙肝的纤维化过程的进展情况进行评估。

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