

· 临床研究 ·

丙种球蛋白治疗扩张型心肌病心力衰竭患者的疗效及免疫研究*

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摘要:目的 观察大量丙种球蛋白治疗扩张型心肌病心力衰竭患者心肌肌凝蛋白重链(CMHC)自身 IgG 抗体滴度的变化及疗效。方法 将 28 例扩张型心肌病心力衰竭患者作为实验组, 其中 14 例在传统治疗基础上加大剂量丙种球蛋白作为治疗组, 其余 14 例为标准对照组, 同时设健康体检者 28 例为健康对照组, 用酶联免疫吸附试验(ELISA)法检测 CMHC 自身 IgG 抗体。结果 未用丙种球蛋白治疗前扩张型心肌病心力衰竭组 CMHC 自身 IgG 抗体与健康对照组比较差异有统计学意义($P < 0.05$); 治疗 12 周后实验组好转 11 例(78.57%), 标准对照组好转 5 例(35.71%), 且治疗组与健康对照组 CMHC 自身 IgG 抗体比较未见明显差异。治疗组左室射血分数由(36.12±9.98)%提高至(46.15±12.18)%, 左室舒张末内径由(59.68±9.60)mm 缩小至(50.05±10.20)mm, 治疗后较标准对照组疗效显著。结论 大量丙种球蛋白治疗扩张型心肌病心力衰竭与传统方法比较疗效明显, 且降低了体内 CMHC 自身 IgG 抗体滴度。

关键词: 心肌病, 扩张型; 心力衰竭, 舒张性; 丙种球蛋白类

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Efficacy and immune of gamma globulin in treatment of dilated cardiomyopathy complicating heart failure*

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Abstract: Objective To observe the anti-cardiac myosin heavy chain IgG changes and efficacy of the antibody titration during the treatment of dilated cardiomyopathy(DCM) complicating heart failure by a large number of gamma globulin. **Methods** 28 inpatients with dilated cardiomyopathy complicating heart failure were taken as the experimental group, 28 cases of healthy examination as the control group. The anti-cardiac myosin heavy chain IgG antibodies were detected by ELISA; moreover, among the patients with heart failure treated by the conventional therapy, 14 cases were selected and added large dose of gamma globulin for observing the curative effect. The remaining 14 cases were taken as the standard control group of this experiment. The anti-cardiac myosin heavy chain IgG antibodies were detected by ELISA. **Results** The anti-cardiac myosin heavy chain IgG antibodies before gamma globulin therapy in the DCM complicating heart failure group had statistical difference compared with the healthy examination group ($P < 0.05$); in the 14 cases of heart failure treated by large dose of gamma globulin, 11 cases (78.57%) in the treatment group were improved, while 5 cases(35.71%) in the standard control group were improved, the anti-cardiac myosin heavy chain IgG antibody had no significant differences between the gamma globulin treatment group and the healthy examination group. The left ventricular ejection fraction(LVEF) in the gamma globulin treatment group was increased from (36.12±9.98)% to (46.15±12.18)%, the left ventricular end-diastolic diameter was decreased from(59.68±9.60) mm to (50.05±10.20) mm, the effects after gamma globulin treatment were more significant than the conventional traditional control group. **Conclusion** Large dose of gamma globulin for treating dilated cardiomyopathy complicating heart failure has more significant effect than the traditional method, reduces the titration of in vivo anti-cardiac myosin heavy chain IgG antibody and contributes to explain the drug action mechanism from immune mechanism.

Key words: cardiomyopathy, dilated; heart failure, diastolic; gamma-globulins

扩张型心肌病心力衰竭是慢性心力衰竭常见的致死性原因, 有研究证实扩张型心肌病与自身免疫有关, 心力衰竭患者血清可检测到包括心肌自身抗体(AMCHA)在内的多种心脏特异性自身抗体, 免疫吸附疗法对扩张型心肌病患者疗效显著。本实验在扩张型心肌病心力衰竭传统治疗的基础上加大大量丙种球蛋白予以冲击治疗, 治疗效果明显, 现报道如下。

1 资料与方法

1.1 一般资料 收集 2011~2012 年本院确诊的扩张型心肌病心力衰竭患者 28 例, 参照 WHO/ISFC 心肌病诊断标准。男 16 例, 女 12 例, 年龄(44.2±10.2)岁。心功能按 NYHA 分级

Ⅳ级 10 例, Ⅲ级 18 例, 其中 14 例为标准对照组(采用常规强心苷、利尿剂、ACEI 类及多巴胺传统方案); 实验组在传统方案上加用大量丙种球蛋白。另选择健康体检者 28 例作为健康对照组, 男 18 例, 女 10 例, 年龄(38±10.4)岁。

1.2 方法 实验组在传统治疗基础上加大丙种球蛋白 400 mg/kg, 静脉滴注, 连用 5 d, 3 个月后观察疗效, 治疗前后均用酶联免疫吸附试验(ELISA)法检测 IgG 抗体。每例入选对象采集肘静脉血 3 mL, 4℃ 3 000 r/min 离心 15 min 分离血清, -70℃ 下冻存, 待测自身抗体。入选病例均于入院后 24 h 内进行超声心动图检查, 评估心功能及测量心脏大小, 治疗 3 个月

后重新评估。

1.3 试剂 人工合成大鼠心肌肌凝蛋白重链(CMHC)部分肽段(1135~1150 位氨基酸残基);BSA-Y-LRSDLSRELEEIS-ERL(由上海楚肽生物技术有限公司合成,高效液相色谱法鉴定其纯度大于 95%)。酶标记抗体:辣根过氧化物酶标记山羊抗人 IgG(北京中杉金桥生物技术有限公司)。

1.4 统计学处理 使用 SPSS 13.0 统计软件进行分析。计数资料用 χ^2 检验,以 $P < 0.05$ 为差异有统计学意义。

2 结果

治疗组治疗 3 个月后,患者症状减轻,如气促减轻、尿量增加、食欲增强。以心功能降低 I 级或左室射血分数升高 5% 为好转,变化不明显者为稳定。治疗组中好转 11 例(78.57%),稳定 3 例。标准对照组好转 5 例(35.71%),稳定 9 例。参选病例治疗期间没有病情加重及死亡发生,治疗组左室舒张末内径(LVEDD)及 LVEF 与标准对照组相比有明显的改善。治疗前后心功能变化见表 1;治疗组未行大量丙种球蛋白治疗前与健康对照组比较 CMHC 自身 IgG 抗体滴定差异有统计学意义($P < 0.05$),用药物治疗后与健康对照组比较差异无统计学意义($P > 0.05$),见表 2。

表 1 两组治疗前后的心功能变化

项目	实验组		标准对照组	
	治疗前	治疗后	治疗前	治疗后
LVEDD(mm)	59.68±9.60 ^d	50.05±10.20 ^{bc}	58.80±9.98	53.30±9.43 ^a
LVEF(%)	36.12±9.98 ^d	46.15±12.18 ^{bc}	36.76±11.04	38.05±10.76 ^c

^a: $P < 0.05$, ^b: $P < 0.01$, ^c: $P > 0.05$, 与治疗前比较; ^d: $P > 0.05$, ^e: $P < 0.01$, 与标准对照组比较。

表 2 治疗组治疗前后与健康对照组 IgG 抗体比较

组别	n	IgG($\bar{x} \pm s$)
健康对照组	28	0.029 8±0.015 1
实验组治疗前	14	0.095 2±0.045 4
实验组治疗后	14	0.030 2±0.020 2

3 讨论

扩张型心肌病是导致心力衰竭的主要心肌疾病之一,其发病率有逐年增长和低龄化趋势,抗心力衰竭治疗是该病治疗的基本方法。随着临床和实验研究的深入,已发现病毒持续感染、免疫应答异常和遗传因素与扩张型心肌病的发生密切相关,尤其近 10 余年来一系列抗心肌自身抗体(包括抗线粒体 ADP/ATP 载体抗体、 β_1 -肾上腺素能受体抗体、抗肌球蛋白抗体等)在该病患者体内的发现及其作用机制的阐明,充分证明自身免疫机制在其发病中起重要作用^[2-3]。线粒体 ADP/ATP 载体抗体和 β_1 -肾上腺素能受体抗体在扩张型心肌病患者中的检出已被证实有较高的敏感性和特异性。因此,抑制上述心肌自身抗体对心肌的损害,针对扩张型心肌病病因与发病机制的治疗已成为该病早期治疗的新靶点。

CMHC 是构成心肌肌凝蛋白(CM)的主要结构。Rose 等^[4]证实心脏特异性自身抗原中包括 CM,它在骨骼肌内不存在,仅在心室细胞内存在,因此 CMHC 亦是心肌免疫损伤中的重要自身抗原,多肽中以 CMHC 抗原表位氨基酸序列合成的作为单一抗原参与自身免疫机制,使心肌病可由心肌炎转化而来^[5-6],且病患部可检测到自身反应性 T 细胞针对其的自身

抗体^[7]。IgG 具有较高亲和力,且在血液中的含量最高,是免疫球蛋白中重要的参与二次免疫应答的类别。本课题组前期动物实验发现^[8],心肌肌球蛋白重链抗体 IgG 亚类是自身免疫反应的标记物之一,这些病理因素可以诱发机体产生自身免疫反应,参与心肌损伤和心室重构,加速心力衰竭的发展。有文献报道,心肌特异性 IgG 亚类自身抗体在扩张型心肌病病程发展中有一定作用^[9]。有实验证实免疫吸附疗法能改善心功能,临床上已有丙种球蛋白治疗扩张型心肌病的方案,丙种球蛋白能中和 β 肾上腺素能受体抗体,细胞因子释放通过其与巨噬细胞 FC-R 结合调节,抑制白细胞和内皮细胞黏附使补体失活,心脏细胞凋亡减轻,有效地调节心力衰竭心肌细胞因子网络的作用,免疫吸附 IgG 抗体而清除抗体,改善心功能及减轻心肌重塑^[10-11]。因此应用丙种球蛋白治疗扩张型心肌病心力衰竭患者有望通过 IgG 抗体变化进一步阐明治疗机制。

本实验通过扩张型心肌病心力衰竭应用大剂量丙种球蛋白治疗与常规治疗相比,疗效显著,患者症状明显减轻,LVEDD 及 LVEF 与对照组相比有明显的改善。且未治疗前扩张型心肌病心力衰竭患者较健康体检组 IgG 抗体滴度差异有统计学意义($P < 0.05$),经治疗后 IgG 抗体滴度差异无统计学意义,说明大量丙种球蛋白能免疫吸附 IgG 抗体使其滴定下调,进而通过该免疫机制减轻心肌细胞凋亡。因此临床应用大量丙种球蛋白治疗扩张型心肌病患者,对于体内、CMHC 自身 IgG 抗体的干预,有望给临床患者提供更好、更安全的治疗方案。

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