

细胞因子白细胞介素-6及胰岛素生长因子-1与类风湿关节炎临床表现的关联性研究

段京明* 王瑞明 李祥双 王璨 孟彩云

安徽省淮北矿工总医院内分泌风湿科 235000

中图分类号: R 593.22 文献标识码: A 文章编号: 1006-7108(2016) 05-0560-04

摘要: 目的 研究白细胞介素-6(interleukin-6, IL-6)及胰岛素样生长因子-1(insulin-like growth factor-1, IGF-1)与类风湿关节炎(rheumatoid arthritis, RA)临床表现的关联性。方法 采用酶联吸附免疫法(enzyme linked immunosorbent assay, ELISA)测定RA患者血清IL-6及IGF-1浓度,分析其于RA临床表现的关联性。结果 1. 骨质疏松组IGF-1水平明显低于无骨质疏松组($P < 0.05$)。而男性组与女性组、RF阳性组与阴性组、ACCP阳性组与阴性组、无+轻度贫血与中度+重度贫血、白细胞减少与白细胞不减少、血小板升高与无血小板升高之间均无显著性差异($P > 0.05$)。2. IGF-1与ACCP滴度、RF滴度、病程、ESR、年龄、CRP均无相关性($P > 0.05$),与疼痛关节数及肿胀关节数呈负相关($P < 0.05$)。3. 男性RA患者IL-6水平明显比女性RA患者水平低($P < 0.05$),ACCP阴性组明显比阳性组低($P < 0.05$),骨质疏松组明显比无骨质疏松组低($P < 0.05$)。而RF阳性组与阴性组、无+轻度贫血与中度+重度贫血、白细胞减少与白细胞不减少、血小板升高与无血小板升高之间均无显著性差异。($P > 0.05$)。4. IL-6水平与ACCP滴度、疼痛关节数及肿胀关节数呈正相关($P < 0.05$),与IGF-1水平呈负相关($P < 0.05$),与RF滴度、病程、ESR、年龄、CRP均无相关性($P > 0.05$)。结论 IL-6及IGF-1与RA病情活动有关。女性患者IL-6高,易于发生骨质疏松。

关键词: 关节炎;类风湿;白细胞介素-6;胰岛素样生长因子-1

The study of the correlation between IL-6/IGF-1 and the clinical manifestations of rheumatoid arthritis.

DUAN Jingming, WANG Ruiming, LI Xiangshuang, WANG Can, MENG Caiyun

Department of Endocrinology, Huaibei General Hospital, Huaibei 235000, Anhui, China

Corresponding author: DUAN Jingming, Email: hbdjm1973@163.com

Abstract: **Objective** To investigate the relationship between interleukin-6 (IL-6)/insulin-like growth factor-1 (IGF-1) and the clinical manifestations of rheumatoid arthritis (RA). **Methods** The enzyme-linked immunosorbent assay was used to determine the serum levels of the IL-6 and IGF-1. **Results** 1) The level of IGF-1 was lower in RA patients with osteoporosis than in those without osteoporosis ($P < 0.05$). The level of IGF-1 was not different between males and females, positive and negative of RF group, positive and negative of ACCP group, patients with non or mild anemia and with moderate or severe anemia, patients with hypoleucocytosis and without hypoleucocytosis, patients with thrombocytosis and without thrombocytosis ($P > 0.05$). 2) The level of IGF-1 was not correlated with the levels of ACCP and RF titers, disease course, ESR, age, and CRP ($P > 0.05$), but was negatively correlated with the number of the pain joint and the swollen joint ($P < 0.05$). 3) The level of IL-6 was lower in males than in females, was lower in ACCP negative group than in ACCP positive group, and was lower in osteoporosis group than in non-osteoporosis group ($P < 0.05$). It was not significantly different between patients with RF factor positive and negative, with non or mild anemia and with moderate or severe anemia, with hypoleucocytosis and without hypoleucocytosis, with thrombocytosis and without thrombocytosis ($P > 0.05$). 4) The level of IL-6 was positively correlated with the number of the pain joint and the swollen joint ($P < 0.05$), negatively correlated with the level of IGF-1 ($P < 0.05$), and not correlated with RF titers, disease course, ESR, age, and CRP ($P > 0.05$). **Conclusion** The action of RA is related to the levels of IL-6 and IGF-1. Females have higher level of IL-6 and are easy to develop osteoporosis.

Key words: Arthritis; Rheumatoid; Interleukin-6; Insulin-like growth factor-1

*通讯作者: 段京明, Email: hbdjm1973@163.com

类风湿关节炎 (rheumatoid arthritis, RA) 是一种引起滑膜炎症, 导致关节破坏, 从而致残性疾病, 我国患病率为 0.32% ~ 0.38%, 发病机制不十分清楚, 基因及环境因素均起重要作用^[1]。而细胞因子在发病过程中起重要作用, 但报道结果不一, 并且与 RA 骨质疏松的关联性报道较少。本研究采用酶联吸附免疫法 (enzyme linked immunosorbent assay, ELISA) 测定 RA 患者血清白细胞介素-6 (interleukin-6, IL-6) 及胰岛素样生长因子-1 (insulin-like growth factor-1, IGF-1) 浓度, 分析与 RA 临床表现的关联性。

1 资料与方法

1.1 一般资料

61 例均来自本院 2012 - 2014 年门诊及住院患者, 其中男 19 例, 女 42 例, 年龄 21 - 80 岁。均排除其他疾病。记录抗环瓜氨酸多肽抗体 (anti-cyclic citrullinated peptide antibody, ACCP)、类风湿因子 (Rheumatoid factor, RF) 滴度、病程、红细胞沉降率 (erythrocyte sedimentation rate, ESR)、年龄、c 反应蛋白 (c-reactive protein, CRP)、IL-6、IGF-1 水平, 白细胞, 血红蛋白, 血小板。

1.2 检测方法

采用 ELISA 测定 IL-6、IGF-1 水平。将所需微孔板放在酶标架上, 室温放置 30 min, 在酶标包被板上设置标准孔 10 孔, 第一孔中分别加标准品 100 μ l, 加标准品稀释液 50 μ l, 混匀, 从第一孔中各取 100 μ l, 分别加到第二孔中, 加标准品稀释液 50 μ l, 混匀, 从第二孔中取 50 μ l, 弃掉, 再取 50 μ l 加到第三孔中, 加标准品稀释液 50 μ l, 混匀, 取 50 μ l, 加到第四孔中, 加标准品稀释液 50 μ l, 混匀, 取 50 μ l 加到第五孔中, 加标准品稀释液 50 μ l, 混匀, 取 50 μ l, 弃掉。在待测样品加样品稀释液 40 μ l, 待测样品 10 μ l, 混匀。37 $^{\circ}$ C 温育 30 分钟, 弃去液体, 加入 1:20 稀释洗涤液加满每孔, 静置 30 s, 弃去, 重复 5 次, 滤纸吸干, 每孔中加入酶标试剂 50 μ l, 空白对照除外, 温育 30 min, 洗涤 5 次, 每孔中加入显色剂 A50 μ l,

再加入显色剂 B50 μ l, 震荡混匀, 避光 15 min, 每孔加终止液 50 μ l, 测定 OD 值, 波长 450 nm。

1.3 统计学方法

组间均数比较用 t 检验或 t' 检验。数值之间关联性用直线相关检验。检验水平 $\alpha = 0.05$ 。

2 结果

2.1 骨质疏松组 IGF-1 水平明显低于无骨质疏松组 ($P < 0.05$)。而男性组与女性组、RF 阳性组与阴性组、ACCP 阳性组与阴性组、无 + 轻度贫血与中度 + 重度贫血、白细胞减少与白细胞不减少、血小板升高与无血小板升高之间均无显著性差异 ($P > 0.05$) (见表 1)。

表 1 两组之间 IGF-1 水平比较 ($\bar{x} \pm s$)

Table 1 Comparison of IGF-1 level between the two groups				
分组	n (例)	IGF-1 (pg/ml)	t	p
性别	男	19 32.9 $\pm$ 42.2	1.57	>0.05
	女	42 53.7 $\pm$ 58.3		
抗 CCP 抗体	阳性	52 46.1 $\pm$ 56.7	0.37	>0.05
	阴性	9 53.6 $\pm$ 40.2		
RF	阳性	48 46.7 $\pm$ 57.7	1.53	>0.05
	阴性	13 49.3 $\pm$ 41.4		
骨质疏松	有	36 26.4 $\pm$ 31.0	4.00	<0.05
	无	25 79.8 $\pm$ 31.0		
贫血	无 + 轻度	52 46.6 $\pm$ 54.7	0.24	>0.05
	中 + 重度	9 51.2 $\pm$ 55.4		
白细胞	减少	6 52.8 $\pm$ 66.8	0.26	>0.05
	正常	55 46.6 $\pm$ 53.5		
血小板	正常	45 44.3 $\pm$ 54.3	0.70	>0.05
	升高	16 55.4 $\pm$ 55.1		

2.2 IGF-1 与 ACCP 滴度、RF 滴度、病程、ESR、年龄、CRP 均无相关性 ($P > 0.05$), 与疼痛关节数及肿胀关节数呈负相关 ($P < 0.05$) (见表 2)。

2.3 男性 RA 患者 IL-6 水平明显比女性 RA 患者水平低 ($P < 0.05$), ACCP 阴性组明显比阳性组低 ($P < 0.05$), 骨质疏松组明显比无骨质疏松组低 ($P < 0.05$)。而 RF 阳性组与阴性组、无 + 轻度贫血与中度 + 重度贫血、白细胞减少与白细胞不减少、血小板升高与无血小板升高之间均无显著性差异。 (P

表 2 IGF-1 与 RA 临床表现的相关性分析

Table 2 The analysis of the relationship between IGF-1 and the clinical manifestations of RF

指标	抗 CCP 抗体 (u/ml)	RF 滴度 (u/ml)	CRP (mg/l)	年龄 (岁)	ESR (mm/h)	病程 (年)	疼痛关节数 (个)	肿胀关节数 (个)
IGF-1								
r	-0.22	-0.06	-0.13	-0.18	-0.01	-0.18	-0.27	-0.27
P	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	<0.05	<0.05

>0.05)(见表3)。

2.4 IL-6水平与ACCP滴度、疼痛关节数及肿胀关节数呈正相关($P < 0.05$),与IGF-1水平呈负相关($P < 0.05$),与RF滴度、病程、ESR、年龄、CRP均无相关性($P > 0.05$)(见表4)。

表3 两组之间IL-6水平比较($\bar{x} \pm s$)

Table 3 Comparison of IL-6 level between the two groups

分组	n	IL-6 (ng/ml)	t	p
性别				
男	19	23.8 ± 25.7	2.51	<0.05
女	42	44.6 ± 37.2		
抗CCP抗体				
阳性	52	41.5 ± 36.7	3.42	<0.05
阴性	9	18.4 ± 13.3		
RF				
阳性	48	40.5 ± 37.8	1.39	>0.05
阴性	13	29.2 ± 21.7		
骨质疏松				
有	36	19.6 ± 18.2	4.25 *	<0.05
无	25	51.0 ± 38.4		
贫血				
无+轻度	52	39.1 ± 36.0	0.50	>0.05
中+重度	9	32.6 ± 31.0		
白细胞				
减少	6	37.9 ± 39.4	0.02	>0.05
正常	55	38.1 ± 35.1		
血小板				
正常	45	37.5 ± 36.1	0.23	>0.05
升高	16	39.9 ± 33.5		

表4 IL-6与RA临床表现的相关性分析

Table 4 The analysis of the relationship between IL-6 and the clinical manifestations of RF.

指标	抗CCP抗体 (u/ml)	RF滴度 (u/ml)	CRP (mg/l)	年龄 (岁)	ESR (mm/h)	病程 (年)	IGF-1	疼痛关节数(个)	肿胀关节数(个)
IL-6									
r	0.50	0.62	0.27	0.46	0.11	0.14	-0.27	0.55	0.51
P	<0.05	>0.05	>0.05	>0.05	>0.05	>0.05	<0.05	<0.05	<0.05

本研究发现,骨质疏松组IL-6水平明显低于无骨质疏松组,Monika等通过托珠单抗治疗RA发现,不仅能降低RA活动指数,并且能阻止放射学进展,提高骨密度^[4]。与本研究相符。IGF-1是一种含有70个氨基酸残基与胰岛素有相似结构的多肽,在骨骼中含量极其丰富,对骨代谢有重要的调节作用:能促进成骨细胞的有丝分裂,还能通过不依赖有丝分裂的途径促进骨基质的合成及矿化。Marc研究发现:在动物模型中IL-6的超表达与GH/IGF-1轴有关。绝大部分活性IGF-1在肝脏中产生,RA患者IGF-1半衰期明显缩短,GH/IGF-1轴活性的降低,打破细胞因子的平衡,在RA发病中扮演重要角色^[5]。吴文等认为:IGF-1通过对抑制胶原酶的表达,从而抑制骨中胶原的降解,影响骨形成,但IGF-1水平与骨量的关系,目前无一致结论。但绝经期妇女IGF-1水平下降可能是发生骨质疏松的重要因素之一^[6]。Sun Hai biao通过对坐骨神经损伤的小鼠注射IGF-1

3 讨论

RA发病机制目前尚不完全清楚,在RA发生发展过程中,细胞因子起重要作用。IL-6有多种功能,当它被激活时,不仅能引起急性炎症反应如引起发热,并且在各种自身免疫性疾病包括RA中起重要作用,在RA患者滑膜组织及血清中均发现高浓度的IL-6,S00-jin chung等研究发现IL-6仅与CRP有关联,IL-6能明显升高DAS28积分^[2],本研究发现IL-6水平与肿胀关节数及疼痛关节数均呈正相关,表明其使患者关节肿痛进一步加重,参与RA的发病,Patick研究发现IL-6与RA患者MCP-1呈正相关,在早期滑膜炎与IL-6明显相关,可能与激活B或T淋巴细胞活性,产生包括CRP等炎症介质有关^[1]。本研究发现女性RA患者IL-6水平明显高于男性患者,可能与女性患者疾病进展较快有关。抗CCP抗体阳性组IL-6水平明显高于阴性组,Michelle发现通过泼尼松治疗能显著降低IL-6水平^[3]。

可以刺激成骨细胞的活性及增加细胞数量,减少骨丢失,研究表明神经损伤可以引起骨平衡破坏,从而引起骨丢失,认为成骨细胞活性受IGF-1受体调节^[7]。Inga lill Engvall研究发现IGF-1能刺激II型胶原的合成并且糖皮质激素能提高IGF-1的活性,在激素治疗RA患者组中IGF-1明显增加,没有激素治疗的患者IGF-1与骨密度呈负相关^[8]。Elisabeth研究发现,IL-1B和TNF-1能减少IGF-1受体酪氨酸磷酸化,从而阻断细胞内活性传导通路^[9]。本研究发现IGF-1水平骨质疏松组明显低于无骨质疏松组,与上述研究相符。Helena通过使用雌激素替代治疗发现能明显降低IL-6受体水平,并且提高IGF-1水平^[10],本研究发现IGF-1与IL-6水平、抗CCP抗体滴度、肿胀关节数、疼痛关节数呈负相关,并且骨质疏松组IGF-1水平明显低于无骨质疏松组,表明IGF-1有阻止RA病情进展的作用。

(下转第569页)

【参考文献】

- [1] 王晨秀,霍亚南,林安华等. 南昌市部分社区40岁以上人群骨质疏松症流行现状调查及影响因素分析[J]. 中国骨质疏松杂志, 2013, 9(8): 850-855.
WANG Chenxiu, HUO Ya'nan, LIN Anhua, et al. Investigation Of the epidemic status of osteoporosis in people over 40 years old in communities in Nanchang and the analysis of the influential factors[J]. Chinese Journal Of Osteoporosis, 2013, 9(8): 850-855.
- [2] 蔡科,范占江. 中老年女性原发性骨质疏松症危险因素[J]. 中国骨质疏松杂志, 2014, 20(9): 1133-1137.
CAI Ke, FAN Zhanjiang. Risk Factors related to primary osteoporosis in middle-aged women[J]. Chinese Journal Of Osteoporosis, 2014, 20(9): 1133-1137.
- [3] 江辉,闫韵飞. 南京地区老年人骨质疏松症危险因素分析研究[J]. 中国骨质疏松杂志, 2012, 18(7): 641-643.
Jiang Hui, Yan Yunfei. Study of risk factors of osteoporosis in elderly population in Nanjing[J]. Chinese Journal Of Osteoporosis, 2012, 18(7): 641-643.
- [4] 马先富,黄振武,杨晓光等. 基于logistic模型对影响绝经期妇女骨质疏松症的动物性饮食因素研究[J]. 中国卫生统计, 2012, 2(2): 206-213.
Ma Xian fu, Huang Zheng wu, Yang Xiao guang, et al. Research on the Effects of Animal Food for Osteoporosis in Postmenopausal Women Based on Logistic Regression[J]. Chinese Journal of Health Statistic, 2012, 2(2): 206-213.
- [5] Chen Y M, Ho S C, Lain S C. Higher sea fish intake is associated with greater bone mass and lower osteoporosis risk in postmenopausal Chinese women[J]. Osteoporos Int, 2010, 21(6): 939-946.
- [6] 谢雁鸣,李建鹏,崔庆荣. 基于多项Logit模型的绝经后骨质疏松症高危人群危险因素分析[J]. 世界科学技术-中医药现代化中医研究, 2012, 14(4): 1835-1840.
Xie Yanming, Li Jianpeng, Cui Qingrong, et al. Analysis on Risk Factors of Postmenopausal Women with High-risk of Osteoporosis Based On Multinomial Logit Model[J]. Science and Technology/Modernization of Traditional Chinese Medicine and Materia Medica, 2012, 14(4): 1835-1840.
- [7] 李欣. 骨质疏松症影响因素的研究回顾[J]. 中国卫生标准管理, 2014, 5(7): 5-6.
Lixin. Research and review the influential factors of osteoporosis [J]. China Health Standard Management. 2014, 5(7): 5-6.

(收稿日期: 2015-09-21)

(上接第562页)

【参考文献】

- [1] Patrick H. Dessein, Ahmed Solomon, Angela J. woodiwiss, et al. Marked Independent Relationship between Circulating Interleukin-6 Concentrations and Endothelial Activation in Rheumatoid Arthritis[J]. Mediators of Inflammation, 2013, http://dx. doi. org/10. 1155/2013/510243.
- [2] Soo-jin Chung, Yong-Jin Kwon, Min-Chan Park, et al. The Correlation between Increased Serum Concentrations of Interleukin-6 Family Cytokines and Disease Activity in Rheumatoid Arthritis Patients[J]. Yonsei Med J, 52(1): 113-120, 2011.
- [3] Michelle J Ormseth, Annette M Oeser, Andrew Cunningham et al. Peroxisome proliferators-activated receptor γ agonist effect on rheumatoid arthritis: a randomized controlled trial[J]. Arthritis Research & Therapy, 2013, 15: R110.
- [4] Monika M Schoels, Desiree van der Heijde, Ferdinand C Breedveld, et al. Blocking the effects of interleukin - 6 in rheumatoid arthritis and other inflammatory rheumatic disease: systematic literature review and meta-analysis informing a consensus statement[J]. Ann Rheum Dis, 2013; 72: 583-589.
- [5] Marc R Blackman, Ranganath Muniyappa, Mildred Wilson, et al. Diurnal secretion of growth hormone, cortisol, and dehydroepiandrosterone in pre-and perimenopausal women with active rheumatoid arthritis: a pilot case-control study[J]. Arthritis Research & Therapy, 2007, 10: R73.
- [6] 吴文,智喜梅,李东风,等. 绝经后妇女骨质疏松患者血清IGF-1、IGFBP-3与骨密度及骨代谢指标的关系[J]. 中国病理生理杂志, 2007, 23(2): 376-378.
WU Wen, ZHI Xi-mei, LI Dong-feng et al. The Relationship between serum IGF-1, IGFBP-3 levels, bone mineral density and bone metabolic markers in postmenopausal patients with osteoporosis[J]. Chinese Journal of Pathophysiology, 2007, 23(2): 376-378. (in Chinese)
- [7] SUN Hai-biao, CHEN Jun-chang. Prevention of bone loss by injection of insulin-like growth factor-1 after neurectomy in rats[J]. Chinese Journal of Traumatology, 2013; 16(3): 156-162.
- [8] Inga-lill Engvan, Bjorn Svensson, Brigitta tengstrand, et al. Impact of low-dose prednisolone on bone synthesis and resorption in early rheumatoid arthritis: experiences from a two-year randomized study[J]. Arthritis Research & Therapy, 2008, 10: R128.
- [9] Elisabeth Bostrom, Mattias Svensson, Sofia Andersson, et al. Resistin and Insulin/Insulin-like Growth Factor Signaling in Rheumatoid Arthritis[J]. Arthritis & Rheumatism, 2011; 63(10): 2894-2904.
- [10] Helena Forsblad d, Elia, Lars-Ake Mattsson, Claes Ohlsson, et al. Hormone replacement therapy in rheumatoid arthritis is associated with lower serum levels of soluble IL-6 receptor and higher insulin-like growth factor 1[J]. Arthritis Research & Therapy, 2003, 5: R202-209

(收稿日期: 2015-10-08)