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类风湿关节炎患者 RF、ANA、CCP、Ig 及炎症因子的水平测定及临床意义

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摘要 目的:探讨类风湿关节炎(RA)患者血清类风湿性因子(RF)、抗核抗体(ANA)、抗环瓜氨酸肽(CCP)抗体、免疫球蛋白(Ig)、补体(C3、C4)以及炎症因子的水平及临床意义。**方法:**收集 2016 年 9 月至 2017 年 4 月我院收治的 165 例 RA 患者为 RA 组,其中 RA 活动期患者 93 例(RA 活动组),RA 缓解期患者 72 例(RA 缓解组),并于同期随机选取 30 例健康体检者为对照组。采用免疫散射比浊法检测各组血清 RF、IgM、IgG、IgA、C3、C4 水平,采用酶联免疫吸附法(ELISA)检测各组血清 CCP 抗体,电化学发光法检测白介素-6(IL-6)、化学发光法检测白介素-8(IL-8)。免疫荧光法检测 ANA。比较不同组别各检测指标水平,并分析 RA 患者 RF、ANA、CCP 抗体、Ig、C3、C4 与炎症因子的相关性。**结果:**RA 活动组、RA 缓解组血清 RF、ANA、CCP 抗体、IgM、IgG、IgA、IL-6、IL-8 水平高于对照组,且 RA 活动组血清 RF、ANA、CCP 抗体、IgM、IgG、IgA、IL-6、IL-8 水平高于 RA 缓解组,差异均有统计学意义($P<0.05$)。RA 活动组、RA 缓解组血清 C3、C4 水平低于对照组,且 RA 活动组血清 C3、C4 水平低于 RA 缓解组,差异均有统计学意义($P<0.05$)。经 Pearson 积矩相关分析,RA 活动期和缓解期患者血清 RF、ANA、CCP 抗体、IgM、IgG、IgA 与炎症因子 IL-6、IL-8 呈正相关关系($P<0.05$),血清 C3、C4 与炎症因子 IL-6、IL-8 呈负相关关系($P<0.05$)。**结论:**RA 患者体内 RF、ANA、CCP 抗体、Ig 及 IL-6、IL-8 水平明显较高,C3、C4 水平明显较低,活动期 RA 患者更为显著,联合检测可早期辅助诊断 RA 及判断病情进展,在临床上具有重要的参考意义。

关键词:类风湿关节炎;类风湿性因子;抗核抗体;抗环瓜氨酸肽抗体;免疫球蛋白;炎症因子

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Determination and Clinical Significance of Levels of RF, ANA, CCP, Ig and Inflammatory Factors in Patients with Rheumatoid Arthritis

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ABSTRACT Objective: To investigate the levels of rheumatoid factor (RF), anti-nuclear antibody (ANA), anti-cyclic citrullinated peptide (CCP) antibodies, immune globulin (Ig), complement (C3, C4) and inflammatory factors in patients with rheumatoid arthritis (RA) and its clinical significance. **Methods:** A total of 165 patients with RA, who were treated in Affiliated Hospital of Traditional Chinese Medicine of Shanghai University of Traditional Chinese Medicine from September 2016 to April 2017, were chosen as group RA, among which, 93 patients were in the RA active phase (RA active group) and 72 patients were in remission stage of RA (RA remission group). 30 healthy volunteers were randomly chosen as control group in the same period. The serum RF, IgM, IgG, IgA, C3, C4 levels in each group were detected by immune scattering Turbidimetry. CCP antibodies in each group were detected by enzyme linked immunosorbent assay (ELISA). The interleukin-6 (IL-6) was detected by electrochemiluminescence assay, while the interleukin-8 (IL-8) was detected by Chemiluminescence. Immunofluorescence was used to detect ANA. The test indexes of different groups were compared. The correlation of RF, ANA, CCP antibodies, Ig, C3, C4 and inflammatory factors in RA patients was analyzed. **Results:** The serum RF, ANA, CCP antibodies, IgM, IgG, IgA, IL-6, IL-8 levels of RA active group and RA remission group were higher than those of control group, and the serum RF, ANA, CCP antibodies, IgM, IgG, IgA, IL-6, IL-8 levels of RA active group were higher than those of RA remission group, the differences were statistically significant ($P<0.05$). The serum C3, C4 levels of RA active group and RA remission group were lower than those of control group, and the serum C3, C4 levels of RA active group were lower than those of RA remission group, the differences were statistically significant ($P<0.05$). The Pearson product moment correlation analysis showed that serum RF, ANA, CCP antibodies, IgM, IgG, IgA in patients with RA active stage and RA remission stage were positively associated with IL-6, IL-8 ($P<0.05$), and the serum C3, C4 were negatively associated with IL-6, IL-8 ($P<0.05$). **Conclusion:** The RF, ANA, CCP antibodies, Ig and IL-6, IL-8 levels in patients with RA are significantly higher, and C3, C4 levels are significantly lower, especially in patients in RA active stage. Combined detection of RF, ANA, CCP antibodies, Ig, C3, C4 and IL-6, IL-8 can be used in the diagnosis and judgment of RA, which has an important reference significance in clinic.

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前言

类风湿关节炎(rheumatoid arthritis, RA)是一种以对称性、多关节炎为主要特征的慢性系统性自身免疫性疾病,发病率0.5%~1.0%^[1-2]。RA并发症较多,可导致手、足以及其它关节发生炎症、僵直、破坏性改变等^[3,4]。RA早期缺乏特异性的临床表现,并且症状复杂多样,很多患者确诊时已错过最佳治疗时间,从而引发关节畸形等不良预后^[5-6]。早发现、早诊断、早治疗是提高患者临床治疗效果,改善预后的重要措施。类风湿因子(rheumatoid factor, RF)、抗核抗体(anti-nuclear antibody, ANA)、抗环瓜氨酸肽抗体(anti-cyclic citrullinated peptide, CCP抗体)、免疫球蛋白(immune globulin, Ig)是临床诊断RA常见的实验室检查指标,研究发现^[7-9],分别检测RF、ANA、CCP抗体、Ig对诊断RA的灵敏度或特异性相对较低,可能出现漏诊和误诊。本研究对RA患者血清中RF、ANA、CCP抗体、Ig(IgM、IgG、IgA)、补体(C3、C4)以及炎症因子水平进行检测,旨在探讨联合检测对诊断RA的临床价值。现报道如下。

1 资料与方法

1.1 一般资料

收集2016年9月至2017年4月我院收治的165例RA患者为研究对象,纳入标准:①符合美国风湿病学会(ACR)制定的RA分类诊断标准^[10];②患者近3个月内未接受糖皮质激素、抗感染药物等可能影响本研究结果的药物治疗。排除标准:①妊娠期和哺乳期的妇女;②心脏功能不全者;③肝、肾功能障碍者;④患有系统性红斑狼疮等可能影响本研究结果的自身免疫性疾病;⑤急、慢性感染性疾病;⑥高血压、糖尿病等慢性疾病;⑦恶性肿瘤患者及精神性疾病患者。165例患者中男性62例,女性103例;年龄39~75岁,平均(46.2±11.9)岁。根据DAS28评分^[11]将RA患者分为RA活动组(活动期RA患者)和RA缓解组(缓解期RA患者),RA活动组93例,男30例,女63例;年龄39~70岁,平均(45.0±12.4)岁。RA缓解组72例,男32例,女40例;年龄41~75岁,平均(47.8±11.1)岁。同期随机选取30例健康体检者为对照组,男13例,女17例;年龄35~79岁,平均(47.6±10.8)岁。RA活动组、RA缓解组、对照

组性别构成比、年龄等基线资料比较,差异无统计学意义($P>0.05$),具有可比性。

本研究获得医院伦理委员会的批准,并且所有研究对象均在知情同意书上签字。

1.2 方法

收集各组研究对象入院时清晨空腹肘静脉血4 mL,在室温环境下静置2 h,以2000 r/min的速度离心10 min,留取血清于-20℃环境下保存,留待检测。采用免疫散射比浊法检测各组血清RF、IgM、IgG、IgA、C3、C4水平,采用酶联免疫吸附法(ELISA)检测各组血清CCP抗体,电化学发光法检测炎症因子白介素-6(IL-6),化学发光法检测白介素-8(IL-8),免疫荧光法检测抗核抗体ANA。涉及的主要试剂和仪器有:贝克曼公司提供BECKMAN COULTER IMMAGE 800全自动分析仪以及RF和Ig检测试剂盒,德国欧蒙公司提供的ANA检测试剂盒、上海科新生物科技股份有限公司提供CCP抗体检测试剂盒,罗氏公司提供Roache Cobas 6000全自动分析仪以及IL-6检测试剂盒,西门子公司提供IMMULITE 1000全自动免疫分析仪以及IL-8检测试剂盒;贝克曼公司提供的台式低速离心机(型号:X-12R型台式冷冻离心机),全自动酶标仪Thermo FC酶标仪(型号:Multiscan FC酶标仪)。

1.3 统计学处理

本研究所有数据均采用SPSS22.0软件录入及统计分析,计量资料的描述采用($\bar{x}\pm s$)表示,多组独立样本的比较采用方差分析,两两比较采用Dunnett-t检验,计数资料的描述采用率(%)表示,比较采用 χ^2 检验,指标之间的相关性采用Pearson积矩相关分析, $P<0.05$ 表示差异有统计学意义。

2 结果

2.1 各组血清RF、ANA、CCP抗体水平比较

三组血清RF、ANA、CCP抗体水平经方差分析,差异有统计学意义($P<0.05$)。两两比较,RA活动组、RA缓解组血清RF、ANA、CCP抗体水平平均高于对照组,且RA活动组血清RF、ANA、CCP抗体水平高于RA缓解组,差异均有统计学意义($P<0.05$)。见表1。

表1 比较各组血清RF、ANA、CCP抗体水平($\bar{x}\pm s$)

Table 1 Comparison of RF,ANA,CCP antibody levels among three groups

Groups	n	RF(U/mL)	ANA(U/mL)	CCP antibody(U/mL)
RA active group	93	39.65±5.86 ^{*#}	132.08±12.24 ^{*#}	33.24±2.50 ^{*#}
RA remission group	72	16.92±6.37 [*]	89.15±11.03 [*]	23.13±2.19 [*]
Control group	30	8.06±5.32	28.62±12.75	5.58±2.64
F	-	16.089	20.334	15.534
P	-	0.000	0.000	0.000

注:与对照组比较,^{*} $P<0.05$,与RA缓解组比较,[#] $P<0.05$ 。

Note: Compared with control group, ^{*} $P<0.05$; Compared with RA remission group, [#] $P<0.05$.

2.2 各组血清 IgM、IgG、IgA 水平比较

三组血清 IgM、IgG、IgA 水平经方差分析, 差异有统计学意义 ($P<0.05$)。两两比较, RA 活动组、RA 缓解组血清 IgM、IgG、IgA 水平均高于对照组, 且 RA 活动组血清 IgM、IgG、IgA 水平高于 RA 缓解组, 差异均有统计学意义 ($P<0.05$); RA 活动

组、RA 缓解组、对照组血清 C3、C4 水平经方差分析, 差异有统计学意义 ($P<0.05$), 两两比较, RA 活动组、RA 缓解组血清 C3、C4 水平低于对照组, 且 RA 活动组血清 C3、C4 水平低于 RA 缓解组, 差异均有统计学意义 ($P<0.05$)。见表 2。

表 2 比较各组血清 IgM、IgG、IgA 水平 ($\bar{x} \pm s$)
Table 2 Comparison of IgM, IgG, IgA levels among three groups

Groups	n	IgM(U/mL)	IgG(U/mL)	IgA(U/mL)	C3(mg/dL)	C4(mg/dL)
RA active group	93	22.16 $\pm$ 4.25**	27.04 $\pm$ 2.28**	6.23 $\pm$ 1.27**	0.96 $\pm$ 0.27**	0.19 $\pm$ 0.11**
RA remission group	72	13.85 $\pm$ 4.91*	16.76 $\pm$ 1.95*	2.59 $\pm$ 1.08*	1.15 $\pm$ 0.33*	0.26 $\pm$ 0.09*
Control group	30	9.22 $\pm$ 5.27	10.34 $\pm$ 2.46	1.12 $\pm$ 0.95	1.52 $\pm$ 0.30	0.37 $\pm$ 0.11
F	-	13.329	10.336	10.185	8.812	8.019
P	-	0.000	0.001	0.001	0.012	0.016

注: 与对照组比较, * $P<0.05$, 与 RA 缓解组比较, ** $P<0.05$ 。

Note: Compare with control group, * $P<0.05$; Compare with RA remission group, ** $P<0.05$ 。

2.3 各组血清 IL-6、IL-8 水平比较

三组血清 IL-6、IL-8 水平经方差分析, 差异有统计学意义 ($P<0.05$), 两两比较, RA 活动组、RA 缓解组血清 IL-6、IL-8 水

平高于对照组, 且 RA 活动组血清 IL-6、IL-8 水平高于 RA 缓解组, 差异均有统计学意义 ($P<0.05$)。见表 3。

表 3 比较各组血清 IL-6、IL-8 水平 ($\bar{x} \pm s$)
Table 3 Comparison of IL-6, IL-8 levels among three groups

Groups	n	IL-6(μ g/L)	IL-8(μ g/L)
RA active group	93	1.34 $\pm$ 0.11**	0.57 $\pm$ 0.05**
RA remission group	72	0.41 $\pm$ 0.09*	0.18 $\pm$ 0.04*
Control group	30	0.16 $\pm$ 0.09	0.09 $\pm$ 0.05
F	-	8.983	8.519
P	-	0.011	0.012

注: 与对照组比较, * $P<0.05$, 与 RA 缓解组比较, ** $P<0.05$ 。

Note: Compare with control group, * $P<0.05$; Compare with RA remission group, ** $P<0.05$ 。

2.4 患者血清 RF、ANA、CCP 抗体、Ig、C3、C4 水平与 IL-6、IL-8 水平相关性分析

经 Pearson 积矩相关分析, 活动期、缓解期 RA 患者血清 RF、ANA、CCP 抗体、IgM、IgG、IgA 与炎症因子 IL-6、IL-8 均呈不同程度正相关关系 ($P<0.05$), C3、C4 与炎症因子 IL-6、IL-8 均呈不同程度负相关关系 ($P<0.05$)。见表 4。

3 讨论

RA 是临床常见的以侵袭关节为主要特征的慢性、进展性自身免疫性疾病, 病理特征包括持续呈进行性的滑膜炎, 以及由其所致的软骨损伤、关节骨侵蚀等, 活动期的 RA 患者临床症状有关节压痛、肿胀、僵硬, 晚期患者因骨质遭到重大破坏和吸收, 而致关节畸形、僵直以及功能障碍, 致残率极高^[12-14]。早发现、早诊断、早治疗是改善患者病情, 促进预后的重要措施。实验室检查指标结合临床表现、X 线平片是诊断 RA 的重要手段^[15, 16]。RF 在 RA 患者体内呈明显高水平, 是临床诊断 RA 最

常见的实验室指标, 但是研究发现 RF 在恶性肿瘤、系统性红斑狼疮等疾病中水平也较高, 可见 RF 缺乏特异性, 极易造成误诊和漏诊, 从而延误对病情的治疗^[17, 18]。

随着医学研究的快速发展, 一系列实验室指标逐渐用于临床辅助诊断 RA, ANA 是用于诊断风湿性疾病等自身免疫性疾病的重要指标, 它在不同疾病中的特征有一定差异, 研究显示^[19], ANA 用于诊断 RA 的灵敏度为 30.0%, 但是特异度却高达 95.0%, 可见, ANA 辅助诊断 RA 有一定价值。CCP 抗体作为一种有病理生理意义的自身抗体, 是 RA 的敏感、特异性指标, 它对 RA 的灵敏度为 65%~80%, 特异度为 90%~99%, 在 2010 年已被纳入 ACR-EULAR RA 的分类诊断标准^[20, 21]。Ig 主要包括 IgM、IgG、IgA 等抗体, 参与了体液免疫环节, 而体液免疫发生紊乱正好与 RA 发病密切相关, 文献报道^[22, 23], 血清 Ig 在 RA 患者血清中明显升高, 并且是评估 RA 病情进展的重要指标。补体 C3、C4 是有重要生物学功能的血清补体成分, 在反复感染、类风湿性关节炎、自身免疫性溶血性贫血等疾病中明显降低,

表 4 患者血清 RF、ANA、CCP 抗体、Ig、C3、C4 水平与 IL-6、IL-8 水平相关性分析

Table 4 Correlation analysis among serum RF, ANA, CCP antibodies, Ig, C3, C4 levels and IL-6, IL-8 levels of the patients

RA	Indexes	IL-6		IL-8	
		r	P	r	P
Active stage	RF	0.671	0.006	0.598	0.001
	ANA	0.608	<0.001	0.712	<0.001
	CCP antibody	0.563	0.002	0.685	<0.001
	IgM	0.592	0.001	0.624	0.002
	IgG	0.736	<0.001	0.709	<0.001
	IgA	0.637	0.001	0.685	<0.001
	C3	-0.592	<0.001	-0.627	<0.001
	C4	-0.467	0.009	-0.593	0.001
Remission stage	RF	0.523	0.003	0.509	0.006
	ANA	0.389	0.011	0.572	0.002
	CCP antibody	0.421	0.008	0.493	0.005
	IgM	0.508	<0.001	0.398	0.012
	IgG	0.611	<0.001	0.517	0.001
	IgA	0.467	0.002	0.468	<0.001
	C3	-0.514	0.001	0.472	-0.001
	C4	-0.473	0.003	-0.385	0.001

其中 C4 水平降低在系统性红斑狼疮更为显著^[24]。IL-6、IL-8 是由内皮细胞、活化的单核巨噬细胞等细胞在病毒感染等外来刺激作用下分泌的炎症因子,具有广泛的生物活性,介导了机体的炎症反应和病理生理过程,RA 患者血管内皮细胞出现损伤会引起机体炎症因子的异常,提示 IL-6、IL-8 可能参与了 RA 的发病过程^[25,26]。

本研究通过检测 RA 患者血清 RF、ANA、CCP 抗体、Ig、C3、C4 以及 IL-6、IL-8 水平,旨在探讨联合检测对 RA 的诊断价值。结果显示,RA 活动组、RA 缓解组血清 RF、ANA、CCP 抗体、IgM、IgG、IgA 水平高于对照组,并且 RA 活动组血清 RF、ANA、CCP 抗体、IgM、IgG、IgA 水平高于 RA 缓解组,说明 RF、ANA、CCP 抗体、IgM、IgG、IgA 参与了 RA 的发病过程,并且与 RA 的病情进展密切相关。有研究认为^[27,28],C3、C4 诊断 RA 无意义,仅能作为了解 RA 病情的客观指标。本研究结果显示,RA 活动组、RA 缓解组血清 C3、C4 水平低于对照组,并且 RA 活动组血清 C3、C4 水平低于 RA 缓解组,与上述研究结果不一致,因此,C3、C4 能否用于辅助诊断 RA 还需要进一步、大样本的研究。结果还显示,RA 活动组、RA 缓解组患者血清 IL-6、IL-8 水平低于对照组,并且 RA 活动组患者血清 IL-6、IL-8 水平低于 RA 缓解组,提示炎症因子 IL-6、IL-8 共同参与了 RA 的病理过程,Terenzi 等人^[29,30]的研究结果显示,IL-6、IL-8 在 RA 发病过程中有重要作用,本研究结果与其一致。经 Pearson 积矩相关分析,活动期、缓解期 RA 患者血清 RF、ANA、CCP 抗体、IgM、IgG、IgA 与炎症因子 IL-6、IL-8 呈相关性,而 C3、C4 与炎症因子 IL-6、IL-8 呈负相关性,提示上

述指标联合检测对早期辅助诊断 RA 及评估患者病情具有重要意义。

综上所述,RA 患者血清 RF、ANA、CCP 抗体、IgM、IgG、IgA、C3、C4 以及 IL-6、IL-8 存在不同程度的异常和改变,联合检测可在早期辅助诊断及评估 RA 患者病情,在临床上有重要的参考价值。

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微创下置管抽吸液化引流术联合依达拉奉治疗脑出血能有效促进患者机体内炎症反应的缓解,促进神经功能的恢复。

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