J Rheumatol R.O.C. 2007;21:46-52

Original Article

The role of synovial fluid levels of anti-cyclic citrullinated peptide antibodies in differential diagnosis of arthritis

Li-Fong Wang[1], Xin-Tian Lin[1], Ling-Ying Lu[1], Jui-Chieh Hu[1], Jui-Cheng Tseng[1], Tsan Yang[2], Chien-Kai Kau[1]

[1]*Division of Allergy, Immunology and Rheumatology, Department of Medicine, Kaohsiung Veterans General Hospital, Taiwan*
[2]*Graduate Institute of Health Care, Meiho Institute of Technology, Taiwan*

Objectives: To determine the usefulness of anti-cyclic citrullinated peptide antibodies (anti-CCP) in synovial fluid (sfCCP) for differential diagnosis of variable arthropathies, and to analyze the correlations with anti-CCP and rheumatoid factor (RF) in serum as well as white blood cells (WBC) counts in synovial fluid.
Methods: 191 synovial fluid samples were tested for WBC counts and anti-CCP using anti-CCP2 assays. Sera of the 43 patients with rheumatoid arthritis (RA) were additionally tested for anti-CCP (smCCP) and RF.
Results: The sfCCP levels were within the normal limit in patients with osteoarthritis, seronegative spondyloarthropathy, gout, Behcet's disease, systemic lupus erythematosus, CPPD disease, infection, osteonecrosis, pigmented villonodular synovitis and undifferentiated connective tissue disease, except one with gout (1/57, 2%). The sfCCP of RA patients were distinctively higher than those in other arthritis groups ($p<0.0001$). The positive rate of sfCCP, smCCP and RF in serum in RA patients was 79% (34/43), 83.7% (36/43) and 72.1% (31/43), respectively. In RA patients, sfCCP was strongly correlated with smCCP ($p<0.001$), RF moderately ($p<0.05$), but not correlated with total WBC, polymorphonuclear cell or mononuclear cell counts in synovial fluid.
Conclusion: sfCCP is highly specific for RA, and is closely related to smCCP and RF, but not correlated to the numbers of PMN, which are considered to offer peptidyl-arginine deiminase 4 and induce citrullinated protein formation in the murine model.

Key words: Anti-CCP antibody, synovial fluid, rheumatoid factor, rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is the most prevalent systemic rheumatic disease, affecting about 1% of the world population. It is characterized by chronic inflammation of the joints, which eventually destroys joints and causes severe disability. Since joint destruction occurs soon after the onset of RA, early aggressive anti-rheumatic therapy is the current strategy. Rheumatoid factor (RF) is presently used in the diagnosis of RA and constitutes one of the criteria proposed by the American College of Rheumatology (ACR) [1]. However, the early diagnosis of RA based solely on ACR criteria and RF can be misleading, especially when initial presentation is atypical. The other consideration is the existence of RF in patients with other autoimmune and infectious diseases, or even in the healthy aged population [2].

Anti-cyclic citrullinated antibodies (anti-CCP), which are developed from serial discovery of anti-

Corresponding Author: Chien-Kai Kau, MD.
Division of Allergy, Immunology and Rheumatology, Department of Medicine, Kaohsiung Veterans General Hospital. 386, Ta-Chung 1st Rd, Tzo-Ying District, Kaohsiung, Taiwan 813
Tel: +886-7-3422121 ext 2103, Fax: +886-7-3455412
Email: ckkau@isca.vghks.tw
Received: July 27, 2007
Revised: August 30, 2007
Accepted: September 15, 2007

perinuclear factor (APF), anti-keratin antibody (AKA), anti-flaggrin, and anti-vimentin (anti-Sa), have attracted interest because of high specificity (92-96.1%) and modest sensitivity (60-63.4%) for diagnosis of RA [3,4]. In order to improve the sensitivity and maintain the specificity of anti-CCP, the second generation of the anti-CCP assay (anti-CCP2), which uses highly reactive peptides that mimic true conformational epitopes selected from the random citrullinated peptide library, was developed [5]. The mean sensitivity of anti-CCP2 can reach 68% (39-94%), which is better than its first generation (anti-CCP1, 53%, range 41-68%), and similar specificity is maintained (95%, range 81-100% for the anti-CCP2 vs. 96%, range 90-99% for the anti-CCP1) [6]. Furthermore, anti-CCP can also predict the development of rheumatoid arthritis in patients with undifferentiated arthritis [7,8].

Not only for diagnosis and prediction of progression, the presence of anti-CCP is also related to prognosis and aggressiveness of RA. Schellenkens et al. first mentioned that the usefulness of baseline anti-CCP and IgM-RF levels to predict erosive disease at 2 years follow-up in RA patients was comparable [9]. Besides, higher levels of anti-CCP were associated with more aggressive disease, higher activity, more erosion and radiological damage as evaluated by the Sharp/Van der Heijde score [10,11].

Although anti-CCP is quite promising for diagnosis and evaluation of prognosis and aggressiveness of RA, relatively low sensitivity is still a concern. In addition, anti-CCP was reported to be detected in some other rheumatic diseases, including hepatitis C infection (HCV) with arthralgia (5.7%, 2 in 35) [12], psoriatic arthritis (PsA) (7.8%, 15 in 192) [13], primary Sjögren's syndrome (pSS) (3%, 1 in 32) [14] and others [15]. Since anti-CCP-secreting B cells were believed to mature at the site of inflammation in RA [16] and with the local presence of citrullinated proteins in RA synovium [17], we hypothesize that anti-CCP in synovial fluid (sfCCP) may provide additional information for differential diagnosis of RA with other arthropathies. Furthermore, because polymorphonuclear cells (PMN) in inflamed synovium can induce peptidyl-arginine deiminase 4 (PAD4) and enhance the formation of citrullination of proteins in murine model [18], we also tried to find if there is any relation between sfCCP and the PMN counts in synovial fluid of RA patients.

Materials and Methods

Patients

191 patients of different rheumatic diseases with complaints of inflamed and swollen joint(s) were evaluated at the rheumatology outpatient department of Kaohsiung Veterans General Hospital. Joint aspiration was performed and the synovial fluid was collected from May, 2005 to June 2006. The diagnoses of RA (n = 43), osteoarthristis (OA, n = 52), seronegative spondyes arthropathy (SpA, n = 13), systemic lupus erythematosus (SLE, n = 1) and Behçet's disease (n = 1) were all confirmed using criteria provided by the American College of Rheumatology (ACR). Undifferentiated connective tissue disease (UCTD, n = 20) was defined as a possible rheumatic disease without clear features of any single disease. Gout (n = 57), CPPD disease (n = 1), infection (n = 1) and pigmented villonedula synovitis (PVNS, n = 1) were confirmed by polarized microscopy, cultures and pathological results. Osteonecrosis (n = 1) was noted on the radiographic studies (Table 1). Sera of RA patients were also collected at the time of joint aspiration. Fresh synovial fluid samples were tested for white blood cell (WBC), polymorphonuclear cell (PMN) and mononuclear cell (MON) counts by hematocytometer. Then the rest were centrifuged and the supernatants were frozen at -80ºC.

Anti-CCP fluoroenzymeimmunoassay

IgG anti-CCP of the synovial fluid and serum was detected by using anti-CCP2 fluoroenzymeimmunoassay (EliA, Sweden Diagnostics, Germany, GmbH). Serial dilutions of serum and synovial fluid were performed according to the manufacturer's instructions. The results were considered to be negative when anti-CCP <7 U/mL, borderline when between 7 and 10 U/mL and positive when >10 U/mL.

RF assay

RF was assayed with a quantitative immunonephelometry test (Beckman IMMAGE, Beckman coulter, Fullerton, Calif.). RF was considered to be negative when the concentration was lower than the cut-off value of the kit (20 IU/mL).

Statistical analysis

ANOVA and Scheffe's post test were used for testing the significance of differences of sfCCP levels among RA and the other 4 groups of arthropathies (OA, gout, seronegative SpA and UCTD). Pearson product-moment correlation, in which sfCCP levels, WBC, PMN, MON counts, serum levels of anti-CCP (smCCP) and RF were

used as independent variables, was performed to analyze their correlations. P value <0.05 was considered to be statistically significant. All the statistics were calculated by using SPSS statistical software.

Results

The demographic features by diagnosis group of the patients were summarized in Table 1. Most of the RA patients in this study were women, whereas the patients with gout, seronegative SpA and UCTD were predominantly men. The OA patients were the oldest among these 5 groups of arthropathies and seronegative SpA patients were the youngest. The mean sfCCP levels, sfCCP positive rates and WBC counts in synovial fluid of different diagnosis groups were in Table 2. Only 1 patient with gout, among all the 4 groups of arthropathies other than RA, was positive for sfCCP . This patient was a case of tophaceous gout with tophi being identified over the left knee, right hand and ankle, which could also be confirmed by radiologic studies. The reason was unknown and the patient did not return for treatment thereafter. The rest of the positive sfCCP cases were all patients of RA and the sfCCP levels were much higher than the other 4 groups, which were statistically significant (p<0.0001). In total, 35/191 synovial fluid samples tested positive for anti-CCP; 43/191 patients were diagnosed with RA; 1/191 was falsely positive. This translated into a sensitivity and specificity of sfCCP for the diagnosis of RA of 79% and 99.5%, respectively. The WBC counts in synovial fluid (sfWBC) of OA patients were significantly lower compared to the other 4 groups of arthropathies (p<0.0001). Otherwise, there was no difference in sfWBC among the other 4 groups of arthropathies.

Table 1. Patient demographics by diagnosis group

	Number (%)	Age (Median)	Sex ratio (M:F)
RA	43 (22.5)	21-84 (57)	9:34
OA	52 (27.2)	36-85 (71.5)	29:23
Gout	57 (29.8)	16-90 (59)	52:5
Seronegative SpA	13 (6.8)	15-78 (25)	12:1
UCTD	20 (10.5)	24-86 (54)	16:4
PVNS	1	21	0:1
Infection	1	58	0:1
CPPD	1	74	0:1
SLE	1	30	0:1
Behcet's disease	1	34	1:0
Osteonecrosis	1	52	0:1
Sum	191	15-90 (62)	119:72

Abbreviations: SpA = spondyloarthropathy,
UCTD = undifferentiated connective tissue disease,
PVNS = pigmented villonodular synovitis

Table 2. Anti-CCP levels and WBC counts in synovial fluid of different rheumatic disorders

	Mean SF anti-CCP (U/mL)	SF anti-CCP (+) rate (%)	WBC in SF
RA	563.36 ± 50.36*	34/43 (79)	23463.15†
OA	1.23	0	861.69
Gout	1.02	1/57 (2)	19370.11†
Seronegative SpA	1.15	0	13413.64†
UCTD	1.36	0	19762.73†
PVNS	0.78	0	
Infection	1.43	0	10450
CPPD	0.49	0	80000
SLE	2.00	0	2000
Behçet's disease	1.88	0	14550
Osteonecrosis	0.60	0	550
Sum		35/191 (18)	

Abbreviations: SF = synovial fluid, RF = rheumatoid factor
Anti-CCP level (IU/mL): <7 negative, 7≤result≤10 borderline, >10 positive
*p<0.0001, when compared RA with OA, gout, seronegative SpA and UCTD
†p<0.0001, when compared with OA
Estimated sensitivity of SF anti-CCP: 79%, specificity of SF anti-CCP: 99.5%

The RA patients were analyzed independently and summarized in Table 3. The RF levels were considered 20 IU/mL when they were less than the cut-off values. In patients with RA, the positive rate of sfCCP and smCCP were similar (79% vs. 83.7%, respectively), and that of RF was 72.1%. When sfCCP and smCCP were considered together, the combined positive rate was 86% (37/43). To evaluate the correlation among the independent variables, the WBC, PMN and MON counts in synovial fluid were listed.

Correlation between synovial fluid anti-CCP and other variables within RA group

There were strong correlations between smCCP and sfCCP ($\gamma^2 = 0.886$, p<0.001), while RF was weakly associated with smCCP and sfCCP ($\gamma^2 = 0.376$ and 0.351, respectively, p<0.05) (Table 4). Nevertheless, sfWBC, PMN and MON counts in synovial fluid (sfPMN, sfMON, respectively) were not correlated with sfCCP, smCCP or RF.

Discussion

Table 3. Demographics of RA patients

No	Sex	Age	sfCCP (U/mL)	smCCP (U/mL)	RF (U/mL)*	sfWBC (/uL)	sfPMN (/uL)	sfMON (/uL)
1	F	78	1878.00	4300.00	1130			
2	F	56	620.00	298.00	237	33600	23184	10416
3	F	81	13.20	22.90	289	22900	21755	1145
4	F	74	324.00	99.80	447			
5	M	54	209.00	175.00	20			
6	F	57	254.00	386.00	989			
7	F	75	594.00	208.00	737			
8	M	52	133.00	69.50	223	36410	32041	4369
9	M	74	229.00	188.00	20	10215	7661	2554
10	M	71	189.00	133.00	415			
11	F	48	6.36	8.26	27.2	2605	2344	261
12	F	61	9.46	44.50	55.2	65000	52650	12350
13	F	62	231.00	216.00	20	26500	16695	9805
14	F	69	558.00	234.00	158	16317	14033	2284
15	F	54	290.00	984.00	359	21750	14355	7395
16	F	58	311.00	569.00	179	49620	39200	10420
17	F	52	2800.00	2080.00	1360	16350	10137	6213
18	F	61	758.00	288.00	20	11450	3778	7672
19	F	55	4.68	4.77	197	5350	3478	1872
20	F	69	337.00	149.00	40.7			
21	F	52	982.00	877.00	28.5	73	1	72
22	F	54	580.00	667.00	439			
23	F	76	1.51	1.63	20			
24	F	48	105.00	389.00	98.6			
25	F	74	0.69	56.90	2010	50400	46368	4032
26	F	44	298.00	995.00	20	135	1	134
27	F	53	9.25	18.30	1560			
28	F	61	772.00	522.00	182			
29	F	36	650.00	440.00	115			
30	F	48	51.60	101.00	23.9			
31	F	55	3060.00	1042.00	272	21100	8229	12871
32	M	57	225.00	194.00	20	17160	11669	5491
33	F	42	1026.00	1680.00	52.1			
34	F	60	439.50	542.00	20	23800	20706	3098
35	M	73	0.45	0.75	20	320	3	317
36	F	84	106.50	126.00	169	23100	19866	3234
37	F	48	5.75	2.97	20	7600	5168	2432
38	F	61	78.50	849.00	61.1	52600	37872	14728
39	F	43	46.30	38.50	287			
40	M	84	2.75	1.00	20	55880	46380	9500
41	F	21	825.00	186.00	166	50160	44141	6019
42	M	76	5200.00	7380.00	1070	9990	9790	200
43	M	51	10.20	0.99	20	3120	1903	1217
Mean			563.36 ± 150.36	617.88 ± 197.71	316.68 ± 71.45	23463.15 ± 723.80	18274.37 ± 167.14	5188.93 ± 852.09
Positive rate			34/43 (79%)	36/43 (83.7%)	31/43 (72.1%)			

Abbreviations: sfCCP = synovial fluid anti-CCP, smCCP = serum anti-CCP, RF = rheumatoid factor, sfWBC = synovial fluid WBC, sfPMN = synovial fluid polymorphonuclear cell, sfMON = synovial fluid mononuclear cell

Anti-CCP level (IU/mL): <7 negative, 7≤result≤10 borderline, >10 positive

*RF (IU/mL): <20 negative, calculated as 20

Anti-CCP is highly specific for RA and possesses moderate sensitivity. Its new generation, anti-CCP2, is even better in sensitivity. Even so, there is still limitation in differentiating rheumatic diseases. Because anti-CCP-

Table 4. Correlations between synovial fluid anti-CCP and other variables in RA group

	sfCCP	smCCP	RF	sfWBC	sfPMN	sfMON
sfCCP		0.866***	0.351*	-0.174	-0.205	0.002
smCCP	0.866***		0.376*	-0.165	-0.158	-0.133
RF	0.351*	0.376*		0.167	0.213	-0.062
sfWBC	-0.174	-0.165	0.167		0.982***	0.719***
sfPMN	-0.205	-0.158	0.213	0.982***		0.576**
sfMON	0.002	-0.133	-0.062	0.719***	0.576**	

Abbreviations: sfCCP = synovial fluid anti-CCP, smCCP = serum anti-CCP, RF = rheumatoid factor, sfWBC = synovial fluid WBC, sfPMN = synovial fluid polymorphonuclear cell, sfMON = synovial fluid mononuclear cell

γ^2 for the numbers

*p<0.05, **p<0.01, ***p<0.001

secreting B cells probably originated from inflammatory sites [16] and because of the presence of citrullinated proteins in synovial tissue [20], we aimed to examine sfCCP levels among various rheumatic diseases and to clarify if sfCCP had diagnostic value in differentiating those arthropathies. In our study, we have revealed that sfCCP levels are significantly higher in the synovial fliud of RA patients in comparison with those with other rheumatic diseases, including seronegative SpA, gout, UCTD and non-inflammatory joint disorders such as OA. None of the sfCCP levels of other rheumatic diseases were above the normal limits, except a case with gout. sfCCP levels were also statistically correlated with smCCP and RF levels, findings which are compatible with previous results raised by Caspi et al. [19].

The detection of anti-CCP in synovial fluid started from the findings by Baeten et al. [17]. They found that citrulline-positive cells in the synovial membrane are highly specific for RA and citrulline-positive cells were detected in 50% of the RA samples but in none of the control patients. Then anti-CCP secreting B cells were identified from peripheral blood, bone marrow, and synovial fluid of RA patients [16]. However, Vossenaar et al. demonstrated that citrullination of synovial antigens is an active process during joint inflammation in both mice and humans, but the induction of autoantibodies directed to these proteins is a more specific phenomenon, detectable only in human RA patients [18]. So in addition to the specific presence of citrulline-positive cells in the synovium, the unique humoral response occurred in RA patients played an even more important role in the pathogenesis of anti-CCP formation. Later the same study group further discovered that the presence of citrullinated proteins is not specific for RA synovial tissue, which suggests that abnormal humoral response, rather than disease-specific expression of citrullinated proteins, characterizes the high specificity of the anti-CCP in RA patients [20].

In addition to a lower positive rate of sfCCP (79%) than smCCP (83.7%) in RA patients, there is also no evidence that sfCCP is superior to smCCP in the diagnosis of RA due to limited information in our study. However, sfCCP still possesses a fair sensitivity (79%) and excellent specificity (99.5%), although the sensitivity of sfCCP seems to be higher than smCCP in other studies, which is around 68% (39-94%) [6]. Nevertheless, it's probably simply a selection bias because only the patients with inflamed joints and joint effusion were enrolled and it also suggests that patients with joint effusion are more likely to test positive for sfCCP. Furthermore, Vossenaar et al. found that sfCCP constituted a 1.4-fold higher proportion of total IgG compared with smCCP [20]. This indicates a local production of the antibodies in joints. Hence, sfCCP to synovial fluid IgG ratio seems to be a potential novel tool for differential diagnosis when sfCCP level is low in patients with RA features. This deserves further study in the future.

PMN in synovial tissue was considered to play a role in the formation of citrullinated protein because in the mouse model, PAD4 is expressed by PMNs infiltrating the synovium during inflammation. The amount of messenger RNA for PAD4 (mPAD4) present in the synovium was consistent with the degree of inflammation. A clear overlap of mPAD4 expression with PMNs was identified, but not with monocytes or macrophages [18]. Expression of the human homolog of rodent PAD4 in human PMNs has been reported and PAD4 expression has been observed in human and mouse peripheral blood PMNs [21]. Therefore, infiltration of PMNs into the synovium seems to be a crucial step in the onset of joint inflammation. Caspi et al. also noticed this association, but they only mentioned the correlation of sfWBC counts with serum and synovial fluid IgA-RF levels, but not with smCCP and sfCCP levels [19]. In this study, only sfCCP, smCCP and serum RF were correlated with each other. No correlation between sfPMN with sfCCP or smCCP could be identified. The crucial roles of PMN were not manifested in our study. Analyzing PMNs in synovial fluid instead of synovium might have brought about these results.

Despite there being some limitations in our study, including fewer variables for comparison, we demonstrate the specific role of sfCCP in the differential diagnosis of RA from other arthritis with a larger sample size and more arthritis groups. The fair sensitivity and

excellent specificity of sfCCP also suggest that it's an ideal tool for differential diagnosis, even though it lacks of evidence of superiority or inferiority in comparison with smCCP or RF. The application of sfCCP/IgG ratio may elucidate the other face of sfCCP and merits further study. We also found that sfCCP, smCCP and RF of RA patients were closely correlated, and especially the first two, but these three were not correlated with sfWBC, sfPMN or sfMON. These findings were not mentioned before and were a little different from the results proposed by Caspi et al. [19]. The relation of PMN and sfCCP and its role in pathogenesis of anti-CCP formation need further investigation in the future.

References

1. Arnett FC, Edworthy SM, Bloch DA et al. The American Rheumatism Association of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
2. van Schaardenburg D, Lagaay AM, Otten HG, Breedveld FC. The relation between class-specific serum rheumatoid factors and age in the general population. Br J Rheumatol 1993;32:546-9.
3. Panchagnula R, Rajiv SR, Prakash J, Chandrashekara S, Suresh KP. Role of anticyclic citrullinated peptide in the diagnosis of early rheumatoid factor-negative suspected rheumatoid arthritis: is it worthwhile to order the test? J Clin Rheumatol 2006;12:172-5.
4. Quinn MA, Gough AK, Green MJ, Devlin J, Hensor EM, Greenstein A, et al. Anti-CCP antibodies measured at disease onset help identify seronegative rheumatoid arthritis and predict radiological and functional outcome. Rheumatology (Oxford) 2006;45:478-80.
5. Riedemann JP, Munoz S, Kavanaugh A. The use of second generation anti-CCP antibody (anti-CCP2) testing in rheumatoid arthritis—a systematic review. Clin Exp Rheumatol 2005;23:S69-S79.
6. Avouac J, Gossec L, Dougados M. Diagnostic and predictive value of anti-cyclic citrullinated protein antibodies in rheumatoid arthritis: a systematic literature review. Ann Rheum Dis 2006;65:845-51.
7. Rantapää-Dagkqvust S, de Jong BAW, Berglin E, Hallmans G, Wadell G, Stenlund H, et al. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. Arthritis Rheum 2003;48:2741-9.
8. van Gaalen FA, Linn-Rasker SP, can Venrooij WJ, de Jong BA, Breedveld FC, Verweij CL, et al. Autoantibodies to cyclic citrullinated peptides predict progression to rheumatoid arthritis in patients with undifferentiated arthritis. Arthritis Rheum 2004;50:709-15.
9. Schellekens GA, Visser H, de Jong BA, can den Hoogen FH, Hazes JM, Breedveld FC, et al. The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. Arthritis Rheum 2000;43:155-63.
10. van der Helm-van Mil AH, Verpoort KN, Breedveld FC, Toes RE, Huizinga TW. Antibodies to citrullinated proteins and differences in clinical progression of rheumatoid arthritis. Arthritis Res Ther 2005;7:R949-58.
11. del Val del AN, Ibanez BR, Fito MC, Gutierrez PR, Loza CE. Anti-cyclic citrullinated peptide antibody in rheumatoid arthritis: relation with disease aggressiveness. Clin Exp Rheumatol 2006;24:281-6.
12. Sène D, Ghillani-Dalbin P, Limal N, Thibault V, can Boekel T, Piette JC, et al. Anti-cyclic citrullinated peptide antibodies in hepatitis C virus associated rheumatological manifestations and Sjögren's syndrome. Ann Rheum Dis 2006;65:394-7.
13. Vander Cruyssen B, Hoffman IEA, Zmierczak H, Van den Berghe M, Kruithof E, De Rycke L, et al. Anti-citrullinated peptide antibodies may occur in patients with psoriatic arthritis. Ann Rheum Dis 2005;64:1145-9.
14. Kamali S, Gurel Polat N, Kasapoglu E, Gul A, Ocal L, Aral O, et al. Anti-CCP and antikeratin antibodies in rheumatoid arthritis, primary Sjögren's syndrome, and Wegener's granulomatosis. Clin Rheumatol 2005;24:673-6.
15. Lee DM, Schur PH. Clinical utility of the anti-CCP assay in patients with rheumatic diseases. Ann Rheum Dis 2003;62:870-4.
16. Reparon-Schuijt CC, van Esch WJE, van Kooten C, Schellekens GA, de Jong BAW, van Venrooij WJ, et al. Secretion of anti-citrulline-containing peptide antibody by B lymphocytes in rheumatoid arthritis. Arthritis Rheum 2001;44:41-7.
17. Baeten D, Peene I, Union A, Meheus L, Sebbag M, Serre G, et al. Specific presence of intracellular citrullinated proteins in rheumatoid arthritis synovium. Arthritis Rheum 2001;44:2255-62.
18. Vossenaar ER, Nijenhuis S, Helsen MMA, van der Heijden A, Senshu T, van den Berg WB, et al. Citrullination of synovial proteins in murine models of rheumatoid arthritis. Arthritis Rheum 2003;48:2489-500.
19. Caspi D, Anouk M, Golan I, Paran D, Kaufman I, Wigler I, et al. Synovial fluid levels of anti-cyclic citrullinated peptide antibodies and IgA rheumatoid factor in rheumatoid arthritis, psoriatic arthritis, and osteoarthritis. Arthritis Rheum 2006;55:53-6.
20. Vossenaar ER, Smeets TJM, Kraan MC, Raats JM, van Venrooij WJ, Tak PP. The presence of citrullinated proteins is not specific for rheumatoid synovial tissue. Arthritis Rheum 2004;50:3485-94.
21. Asaga H, Nakashima K, Senshu T, Ishigami A, Yamada M. Immunocytochemical localization of peptidylarginine deiminase in human eosinophils and neutrophils. J Leukoc Biol 2001;70:46-51.

關節液內的抗環狀瓜氨酸抗體濃度在關節炎鑑別診斷的角色

王立峰[1] 林新田[1] 呂聆音[1] 胡瑞潔[1] 曾瑞成[1] 楊燦[2] 高堅凱[1]

[1]高雄榮民總醫院 過敏免疫風濕科

[2]美和技術學院 健康照護研究所

目的：評估關節液抗瓜氨酸抗體濃度在關節炎鑑別診斷上的效用，並分析此抗體與血中的抗瓜氨酸抗體與類風濕因子濃度，及關節液中白血球數量的關係。方法：從單一醫學中心的關節炎門診患者中收集191個關節液檢體，分析其中的抗瓜氨酸抗體濃度與白血球數目與分類，類風濕性關節炎患者則加作血中的抗瓜氨酸抗體與類風濕因子濃度。結果：在退化性關節炎、血清陰性脊椎關節炎、痛風、貝塞特氏症、全身性紅斑狼瘡、結晶性關節炎、感染性關節炎、骨缺血性壞死、色素沉著性滑液膜結節絨毛樣增生與待分類結締組織疾患患者的關節液中，只有一例痛風患者抗瓜氨酸抗體濃度異常(2%, 1/57)，其餘皆在正常值範圍內。類風濕性關節炎患者的關節液中，抗瓜氨酸抗體濃度顯著高於其他關節炎的檢體($p<0.0001$)。關節液抗瓜氨酸抗體濃度、血中的抗瓜氨酸抗體與類風濕因子濃度在類風濕性關節炎患者中的陽性率分別爲79% (34/43)、83.7% (36/43)及72.1% (31/43)。關節液抗瓜氨酸抗體濃度在診斷類風濕性關節炎上，可達理想的敏感度(79%)與優異的特異性(99.5%)。在類風濕性關節炎患者中，關節液抗瓜氨酸抗體濃度和血中的抗瓜氨酸抗體有強正相關($p<0.001$)，和類風濕因子濃度有弱正相關($p<0.05$)，但和關節液中白血球數量，不管是多核球或單核球，都不相關。結論：關節液抗瓜氨酸抗體濃度和血中的抗瓜氨酸抗體一樣，在診斷類風濕性關節炎具有高特異性，且其關節液中的濃度與血中的濃度呈強正相關，和血中類風濕因子濃度呈弱正相關，但和關節液中的多核球數量不相關，這和文獻上所提, 多核球可促進蛋白質瓜氨酸化，並誘發抗體反應的說法有出入。

關鍵詞：抗環狀瓜氨酸抗體、關節液、類風濕因子、類風濕性關節炎