MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2017; 23: 4312-4320
DOI: 10.12659/MSM.905880

Received: 2017.06.22
Accepted: 2017.08.13
Published: 2017.09.07

Analysis of Antineutrophil Cytoplasm Antibody from 118 730 Patients in Tertiary Hospitals in Jiangxi Province, China

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Background: The discovery of antineutrophil cytoplasm antibody (ANCA) makes the early diagnosis of primary vasculitis possible, and also has important guiding significance for the diagnosis and treatment of secondary vasculitis. This study aimed to investigate the clinical significance of ANCA.

Material/Methods: ANCA was detected by indirect immunofluorescence assay (IIF), and anti-myeloperoxidase (MPO) antibody, and anti-proteinase 3 (PR3) antibody were detected by ELISA. The results were analyzed retrospectively.

Results: Among 118 730 patients, a total of 5853 (4.93%) were positive for ANCA. In the positive cases, 3.98% were male and 6.33% were female, with significant differences (χ^2=123.38, P<0.01). For ANCA, the department with the highest positive rate (15.06%) was the Department of Rheumatology, followed by 7.78% in the Department of Dermatology, 6.79% in the Department of Nephrology, and 5.72% in the Department of Traditional Chinese Medicine (TCM). Anti-PR3 and cANCA were highly specific in primary vasculitis (*P*<0.01). Anti-MPO and pANCA had high specificity for other autoimmune diseases (*P*<0.01).

Conclusions: ANCA has important guiding significance for vasculitis-related diseases. Therefore, it is important in the diagnosis and treatment of this disease and has value in clinical practice.

MeSH Keywords: Antibodies, Antineutrophil Cytoplasmic • Autoimmune Diseases • Vasculitis

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/905880

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Background

Antineutrophil cytoplasmic antibodies (ANCA) are autoimmune antibodies against neutrophil cytoplasmic components, and has become a specific serological marker antibody for systemic vasculitis represented by Wegener's granulomatosis (WG) in recent years. ANCA, as an important serological diagnosis of vasculitis, is widely recognized by the medical profession for its usefulness in assessing the remission and recurrence status of diseases.

ANCA is divided into cANCA and pANCA, and the matrix tablets for detection of ANCA include ethanol-immobilized neutrophils, formalin-fixed neutrophils, HEP-2 cells, and monkey liver tissues, the latter 2 are mainly to exclude ANA interference in the detection. The main target antigen of pANCA is anti-myeloperoxidase (MPO). MPO is a highly cationic protein with a molecular weight of 146 000, which can cause continuous ribbon fluorescence in the periphery of neutrophils. The main target antigen of cANCA is anti-protease 3 (PR3), which can cause the whole cytoplasmic region of neutrophils to cover coarse particles.

Primary vasculitis is a not yet clear etiology of a class of small vasculitis, mainly violations of small blood vessels, such as small arteries, arteries, vascular wall necrosis inflammation, cellulose-like necrosis as a pathological feature, is a class of sexually transmitted autoimmune diseases. Primary vasculitis generally refers to microscopic multiple vasculitis (MPA), Wegener's granulomatosis (WG), Churg-Strauss syndrome (CSS), and primary necrosis crescentic glomerulonephritis (NCGN). Clinically, WG, MPA, CSS, NCGN, and other series of diseases are called ANCA-related systemic vasculitis (AASV). AASV is a kind of small vascular wall inflammation and/or fibrinoid necrosis, and is the pathological basis of a group of autoimmune diseases, mainly involving systemic small vessel autoimmune disease, and is the most common adult primary vasculitis. ANCA and its target antigen are widely used in clinical practice, and the incidence of AASV is increasing. In this paper, the results of ANCA testing in 118 730 cases in tertiary care hospitals in Jiangxi Province, China, from January 2014 to December 2016 were retrospectively analyzed.

Material and Methods

Review of the cases

Retrospective statistical analysis was completed in tertiary (3A) hospitals of Jiangxi Province from January 2014 to December 2016. Of the total of 118 730 cases with ANCA test results, there were 23 720 cases from the Second Affiliated Hospital of Nanchang University, 33 770 cases from the First Affiliated Hospital of Nanchang University, 18 cases from Jiangxi Provincial People's Hospital, 1630 cases from Jiangxi Provincial Hospital of Traditional Chinese Medicine, 3890 cases from the Fourth Affiliated Hospital of Nanchang University, 6510 cases from the Affiliated Hospital of Jiujiang University, 8480 cases from Yichun People's Hospital of Jiangxi Province, 10 070 cases from the Affiliated Hospital of Gannan Medical University, 7580 cases from Ganzhou People's Hospital of Jiangxi Province, and 5060 cases from Pingxiang People's Hospital of Jiangxi Province. There were 41 633 men and 77 097 women in total and the ratio of males to females was 1: 1.85. Ages ranged from 1 to 109 years old, with an average of 51.5±12.1 years. Positive results appeared in 5853 cases, in which 2053 were vasculitis, including Wegener's granuloma (696 cases), microvascular polyvascular (659 cases), eosinophilic granulomatous vasculitis (173 cases), nodular polyarteritis (251 cases), aorta arteritis (121 cases), IgA vasculitis (53 cases), and Behçet's disease (54 cases). Among the positive cases, 3612 had other autoimmune diseases, including 54 cases of autoimmune hepatitis, 115 cases of primary biliary cirrhosis, 98 cases of primary sclerosing cholangitis, 825 cases of rheumatoid arthritis, 1182 cases of systemic lupus erythematosus, 565 cases of ulcerative colitis, 404 cases of mixed connective tissue disease, 82 cases of scleroderma, 287 cases of Sjögren's syndrome, 75 cases of type 2 diabetes mellitus, and 188 cases of other types of diseases. We selected 100 healthy participants as the control group. Written informed consent was obtained from all subjects. The diagnosis of vasculitis was based on the diagnostic criteria of vasculitis [1], and rheumatoid arthritis and systemic lupus erythematosus and other autoimmune diseases were diagnosed according to the standards established by the American Society of Rheumatology (ACR) [2]. All specimens were obtained with the patient's informed consent and approved by the Hospital Ethics Committee.

Instruments and reagents

Many types of fluorescence microscopes were used, including EUPOStar Plus, Nikon, and OLYMPUS BX. Microplate readers used included SUNRISE, ELX 808, and Multiscan MK3. Washing machines used included PW-960 automatic, ELX 50, and BioTek automatic. Reagents used were the antineutrophil cytoplasmic IgG test kit, Anti-MPO assay kit, and the anti-PR3 assay kit provided by EUROIMMUN (Germany).

Methods

ANCA fluorescence pattern was determined by IIF method. Reagents were purchased from EUROIMMUN Company (Germany). The reaction areas included HEp-2 cells, primate liver tissue, and formaldehyde- and ethanol-fixed human neutrophils. Samples were diluted with PBST buffer for 1: 10 dilution and tested in strict accordance with the EUROIMMUN

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Table 1. ANCA test results.

	Number of cases	Number of positive cases	Positive rate (%)
Male	41633	1657	3.98
Female	77097	4196	6.33
Total	**118730**	**5853**	**4.93**
χ^2		123.38	
P		<0.01	

The χ^2 test was used, and the results showed that ANCA-positivity was associated with sex (χ^2=123.38, *P*<0.01).

Table 2. Departmental distribution with cases positive for ANCA.

Department	Number checked	Positive number	Positive rate (%)	Department	Number checked	Positive number	Positive rate (%)
Rheumatology	28894	4352	15.06	Department of Infectious Diseases	3720	134	3.60
Nephrology	20350	1382	6.79	Pediatrics	808	34	4.21
Neurology	11210	255	1.79	Traditional Chinese Medicine	4723	270	5.72
Gastroenterology	12100	471	3.89	Dermatology	1207	94	7.78
Hematology	10732	328	3.06	Geriatrics	721	35	4.85
Respiratory medicine	11906	576	4.84	General surgery	140	20	1.43
Painful disease	980	24	2.45	Outpatient	10239	655	6.39

titration plate technique. The above steps were in strict accordance with the reagent manual and the standard operating procedure (SOP) in our laboratory.

Human serum anti-MPO and anti-PR3 antibodies were tested by enzyme-linked immunosorbent assay (ELISA) method. Reagents were from EUROIMMUN Company. The samples were diluted, then the diluted sera, negative control, positive control, and blank control were added to the microwells. The platelets were incubated for 30 min at room temperature. After incubation, plates were washed. Human IgG bound on the plates was detected by horseradish peroxidase-conjugated antibody using tetramethylbenzidine (TMB) as a peroxidase substrate. The reaction was stopped by the addition of 2 M H_2SO_4, and the absorbance was read at 450 nm. The above steps were in strict accordance with the reagent manual and the SOP.

Statistical analysis

Statistical analyses were performed using SPSS 19.0 (SPSS for Windows, ver. 19.0). Quantitative variables are presented as mean ±SD. The validity was checked using the rank sum test. The χ^2 test was used to compare categorical variables. *P*<0.05 was considered as statistical significance.

Results

The analysis of total positive rate

Among 118 730 cases with ANCA test results, there were 5853 positive cases. There was a significant difference between the positive male and positive female groups (χ^2=123.38, *P*<0.01) (Table 1).

The departmental distribution of the 5853 cases positive for ANCA

The department with highest positive rate was the Department of Rheumatology, which was consistent with the specificity of ANCA-positive status in vasculitis patients treated in this department (Table 2).

Test results of anti-PR3, anti-MPO, and ANCA antibody in 5853 positive cases

Anti-PR3 and cANCA pattern were highly specific in vasculitis. The anti-MPO and pANCA pattern had high specificity for other autoimmune disease (Table 3).

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Table 3. The results of anti-PR3, anti-MPO, and ANCA antibody in 5853 cases.

Group	Number of cases	Anti-PR3-positive		Anti-MPO-positive		ANCA-positive			
						cANCA-positive		pANCA-positive	
		Number of cases	%	Number of cases	%	Number of cases	%	Number of cases	%
Vasculitis	2053	748	41.31	708	29.61	667	32.49	760	37.02
Other autoimmune diseases	3612	457#	12.65	2140#	59.25	329#	9.11	2779#	79.94
Other	188	45	23.94	105	55.85	50	26.60	106	56.38
Healthy physical examination group	100	0*	0.00	0*	0.00	0*	0.00	0*	0.00
Total	5953	1295	21.75	3062	51.44	1096	18.41	3751	63.01

* Compared with vasculitis and autoimmune diseases, by χ^2 test, *P<0.01*, the results had a very significant significance. # Compared with vasculitis, by χ^2 test, *P<0.01*, the results had a very significant significance.

Table 4. MPO antibody and anti-PR3concentration test results.

Group	Number of cases	Anti-PR3-positive		Anti-MPO-positive	
		Number of cases	Concentration (IU/ml)	Number of cases	Concentration (IU/ml)
Vasculitis	2053	748#	31.65±17.75	708#	47.23±21.58
Other autoimmune diseases	3612	457	18.22±10.91	2140	74.58±41.10
Other diseases	188	45	6.28±3.39	105	7.48± 7.86

Compared with other autoimmune diseases, the results were very significant (*P*<0.01) in the rank sum test.

Comparison of the concentration of anti-PR3 and anti-MPO antibody in autoimmune diseases

In the vasculitis group, the concentration and positive rate of anti-PR3 antibody was highest, and in other autoimmune diseases the concentration and positive rate of anti-MPO antibody was highest, as shown in Table 4.

The positive rate in the different types of diseases positive for ANCA

The positive rate of ANCA in vasculitis was higher than that in other autoimmune diseases. The positive rate of Wegener's granuloma was the highest in the vasculitis group (71.60%). The positive rate of systemic lupus erythematosus was the highest (6.13%) in the other autoimmune diseases group (Table 5).

The positive rate of anti-PR3 and anti-MPO antibody and 2 patterns of ANCA in different diseases

In the group with vasculitis, Wegener's granulomatosis had the highest positive rate of anti-PR3 (75.41%) and cANCA (67.96%). Microscopic vasculitis had the highest positive rate of anti-MPO antibodies (54.32%) and pANCA (57.51%). In the group of other autoimmune diseases, systemic lupus erythematosus (SLE) had the highest positive rate of anti-MPO (86.13%) and pANCA (87.73%). Data are shown in Table 6.

Organ involvement accompanied by 2 patterns of ANCA antibody

The positive rate of pANCA was higher than that of cANCA in cases of kidney involvement, liver involvement, ear involvement, nasal involvement, muscle involvement, nerve system involvement, and digestive tract involvement. The positive rate of cANCA was more than that of pANCA in cases of eye involvement and joint involvement. See details in Table 7.

Clinical evaluation of anti-PR3, anti-MPO, cANCA, and pANCA

Anti-PR3 and cANCA were more sensitive and specific, as shown in Table 8.

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Table 5. The 5853 cases with ANCA-confirmed clinical diagnosis and positive rate.

Disease type	Detection of total number of cases	Number of positive cases	Positive rate (%)
Vasculitis			
WG	972	696	71.60
MPA	983	659	67.03
CSS	317	173	54.57
PAN	572	251	43.88
TA	298	121	40.60
IgAV	251	99	39.44
BD	220	54	24.55
Other autoimmune diseases			
AIH	7655	54	0.71
PBC	6008	115	1.91
PSC	7434	98	1.32
RA	21773	825	3.79
SLE	19297	1182	6.13
UC	10450	565	5.41
MCTD	10358	404	3.90
PSS	7026	82	1.17
SS	7572	287	3.79
T2DM	12541	75	0.60
Other diseases	5003	113	2.25
Total	**118730**	**5853**	**4.93**

Discussion

In 1982, Davies [4] detected an IgG type of antibody in patients with segmental necrotizing glomerulonephritis in serum by the IIF method. The antibody antigen is neutrophil cytoplasmic antigen, so it is called ANCA. Later, Van der Woude [5] confirmed the presence of ANCA in serum of patients with Wegener's granulomatosis and identified a specific serological diagnostic value. The important clinical role of ANCA was recognized.

We retrospectively analyzed the test results of 118 730 cases in tertiary hospitals for ANCA from January 2014 to December 2016 in Jiangxi Province. There were 5853 positive cases (4.93%), which is similar to rates in Chinese and foreign reports. For the positivity of ANCA, the male-to-female ratio was 1: 1.85, which is consistent with the literature [6–11].

The department with the highest positive rate (15.06%) of ANCA was the Department of Rheumatology in tertiary care hospitals in Jiangxi Province, which is consistent with the specificity of ANCA in rheumatism. The positive rate in dermatology was up to 7.78%, because a common complication of vasculitis is skin rash. The renal positive rate can be up to 6.79%, which is related to ANCA-associated vasculitis, mainly involved in kidney disease, such as rapid progressive glomerulonephritis and necrotic crescentic nephritis [12–14].

Among 2053 cases of vasculitis and 3612 cases of other autoimmune diseases, anti-PR3 and cANCA were highly specific in vasculitis. Anti-MPO and pANCA had high specificity for other autoimmune diseases, which is consistent with the literature [25–31. There were 748 cases of vasculitis patients with anti-PR3 concentrations of 31.65±17.75 IU/ml, with significant differences compared with the other autoimmune diseases group. It may be concluded that anti-PR3 in vasculitis

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Table 6. Positive rate of anti-MPO, anti-PR3 antibody, and 2 patterns of ANCA in different diseases.

Disease types	Number of cases	Anti-PR3-positive		Anti-MPO-positive		ANCA-positive			
						cANCA-positive		pANCA-positive	
		Number of cases	%	Number of cases	%	Number of cases	%	Number of cases	%
Vasculitis									
WG	696	523	75.14	24	3.45	473	67.96	13	1.88
MPA	659	101	15.33	358	54.32	84	12.75	379	57.51
CSS	173	18	10.40	90	52.02	15	8.76	95	54.91
PAN	251	22	8.76	125	49.80	22	8.76	142	56.57
TA	121	59	48.76	35	28.92	44	36.36	49	40.49
IgAV	99	23	23.23	42	44.44	25	25.25	46	46.46
BD	54	2	3.70	22	40.74	4	7.41	26	48.15
Other autoimmune diseases									
AIH	54	3	5.56	27	50.00	5	9.26	33	6.11
PBC	115	12	10.43	55	47.83	9	7.83	78	67.83
PSC	98	1	1.02	52	53.06	0	0	56	57.14
RA	825	223	27.03	251	30.42	119	14.42	704	85.33
SLE	1182	20	1.69	1018	86.13	27	2.28	1037	87.73
UC	565	29	5.13	361	63.89	22	3.89	454	80.35
MCTD	404	110	27.23	141	34.90	112	27.72	169	41.83
PSS	82	5	6.10	10	12.20	2	2.43	17	20.73
SS	287	54	18.82	225	78.40	33	11.50	231	80.49
T2DM	75	17	22.67	35	46.67	19	25.33	40	53.33
Other	113	28	24.78	70	61.95	31	27.43	66	58.41

has a high degree of specificity. There were 457 cases of other autoimmune diseases with anti-MPO antibody concentration of 74.58±41.10 IU/ml, and there were significant differences from the vasculitis group. MPO antibody was highly specific in other autoimmune diseases. This result is consistent with previous studies [32–41].

Initially, it was found that ANCA existed in the sera of patients with primary vasculitis. As the study of ANCA became more comprehensive, and with the wider clinical use of ANCA, the value of ANCA in diagnosis and prognosis of diseases is increasingly recognized in the medical field. ANCA can be divided into cANCA and pANCA according to the different patterns of immunofluorescence. Some target antigens and some patterns of ANCA are recognized to have a close relationship with some diseases. In our study, anti-PR3 and cANCA were mainly seen in Wegener's granuloma, while anti-MPO and pANCA were mostly seen in microscopic multiple vasculitis. This result is slightly different from Martínez Téllez [42] because the Chinese and Western ANCA-related target antigen corresponding to the disease is different. ANCA contains a variety of antigenic components: mainly anti-MPO and anti-PR3. Additionally, among 5853 patients positive for ANCA, we did not detect anti-MPO or anti-PR3 antibodies in 1034 patients, indicating that in addition to the 2 common target antigens, there were other antigens present, including lysozyme, cathepsin, elastase, and lactoferrin, which is consistent with the literature [43–50]. Further confirmation of other specific target antigens needs to be confirmed.

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Table 7. Organ involvement related with pANCA and cANCA.

Type of involvement	Total number of cases	cANCA-positive (1046)		pANCA-positive (3645)		χ^2
		Number of cases	Positive rate (%)	Number of cases	Positive rate (%)	
Kidney involvement	1484	283#	27.06	1201	32.95	0.67
Liver involvement	1397	209#	19.98	1188	32.59	159.36
Eye involvement	342	121#	11.57	221	6.06	36.43
Ear involvement	354	65*	6.21	299	8.20	4.14
Nasal involvement	279	33#	3.15	215	5.90	8.12
Joint involvement	544	129*	12.33	415	11.39	5.78
Muscle involvement	438	71#	6.79	367	10.07	10.34
Nervous system involvement	268	44*	4.21	224	6.15	5.57
Digestive tract involvement	741	101#	9.66	640	17.56	38.16
Other organs involved	69	24*	2.29	45	1.23	6.30

* Compared with pANCA, the results were significant by χ^2 test ($P<0.05$). # Compared with pANCA, the results are very significant by χ^2 test ($P<0.01$).

Table 8. Clinical evaluation of anti-PR3, anti-MPO antibody, and ANCA results.

Test items	Sensitivity (%)	Specificity (%)	Prevalence (%)	Positive predictive value (%)	Negative predictive value (%)	Positive likelihood ratio (%)	Negative likelihood ratio (%)
Anti-PR3	62.02	70.74	21.27	36.43	87.35	2.12	53.69
Anti-MPO	24.86	52.25	50.27	34.49	40.75	0.52	143.81
cANCA	66.97	70.31	17.58	32.49	90.89	2.26	46.98
pANCA	21.47	39.18	62.27	37.02	23.06	0.35	200.43

In 5853 cases with positive results for ANCA, 2053 cases were diagnosed with vasculitis. PR3-ANCA in Wegener's granuloma had a significant positive rate of 75.14%, while the positive rate of MPO-ANCA was 54.32% in microscopic multiple vasculitis. It was slight lower compared with the results from Zhang [51], and there is a huge difference between the distribution of patients in different cities and using different detection methods. Eosinophilic granulomatous vasculitis in AAV is rare, and this might be related to the low incidence rate in China, and is in line with the literature [52–59]. In 3612 cases of other autoimmune diseases, clinical diseases were mainly SLE-based (20.19% positive) and RA-based (14.10% positive), and given priority to anti-MPO and pANCA. Ulcerative colitis is a type of autoimmune disease with a high positive rate. The anti-MPO and pANCA had a high specificity, which is basically consistent with previous reports [60,61].

ANCA-associated vasculitis mainly involves the kidneys and liver. The positive rate can be up to 25.35% and 23.87%. In addition, the involvement of joints, muscles, nervous system, and digestive tract suggest multi-organ involvement. The positive rate of pANCA was higher than that of cANCA in cases involving the kidneys, liver, ears, nose, muscles, nerves, and digestive tract. The positive rate of cANCA was higher than that of pANCA in cases of eye involvement and joint involvement, consistent with the literature [62,63]. Organ involvement with ANCA-associated vasculitis has a variety of clinical manifestations, resulting in different diseases. Hence, this characteristic causes various difficulties in clinical diagnosis, which need to be explored in greater detail.

There were some limitations to the present study. The first is the limitations of indirect immunofluorescence interpretation. According to the different staining sites of immunofluorescence, ANCA can be divided into cANCA and pANCA. Each

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hospital has subjective factors when reading data from the fluorescent microscope. The second is the limitations of the target antigen. The 2 major target antigens of ANCA are anti-MPO and anti-PR3 (as studied in this paper). However, there are many ANCA-associated target antigens, and the diseases associated with these target antigens in this study are included in the "other diseases" because of the small clinical base, which is not covered in this article and needs further studies. The last one is the limitations of the study object. The clinical data, which was collected from China, were slightly different from the foreign reports.

Conclusions

ANCA enables early diagnosis and treatment of primary vasculitis. With the development of ANCA detection, and as detection technology improves, the detection rate of ANCA in diseases is increasing and more types of diseases can be detected through this method. Therefore, much more attention should be paid to ANCA in the diagnosis of clinical disease.

Acknowledgement

We thank the Clinical Laboratory of Tertiary Hospitals in Jiangxi Province to provide their data, including the Second Affiliated Hospital of Nanchang University, the First Affiliated Hospital of Nanchang University, Jiangxi Provincial People's Hospital, Jiangxi Provincial Hospital of Traditional Chinese Medicine, the Fourth Affiliated Hospital of Nanchang University, the Affiliated Hospital of Jiujiang University, Yichun People's Hospital of Jiangxi Province, the Affiliated Hospital of Gannan Medical University, Ganzhou People's Hospital of Jiangxi Province, and Pingxiang People's Hospital of Jiangxi Province.

Conflict of interest

None.

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