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Assessment of the Efficiency of Methods of Diagnosis of Different Types of Polyangiitis Granulematosis

Berdieva D. U.[1], Rizamukhamedova M. Z.[1], Tashpulatova M. M.[1], Ziyayeva F. K.[1], Nurmukhamedova N. S.[2], Ibragimova N. X.[3]

[1]Department of Faculty and Hospital Therapy №1 with Course of Professional Pathology of Tashkent Medical Academy of Uzbekistan
[2]Department of Internal Disease №2 with Endocrinology of Tashkent Medical Academy of Uzbekistan
[3]PhD, Head of Military Polyclinic of Uzbekistan

Abstract Early diagnosis of polyangiitis granulomatosis (PAG) is a difficult clinical task and requires a thorough examination of the patient using modern research methods to identify pathognomonic symptoms. With rhinoscopy, laryngoscopy, nasopharyngeal cavity and computed tomography of the lungs, it is necessary to purposefully look for damage to the respiratory tract, because for a long time the disease can be asymptomatic or accompanied by little clinical symptoms. In only 50% of patients, the diagnosis is made within the first 3-6 months from the onset of the disease, and in 7%, PAG remains undiagnosed for 5-16 years from the onset of the first symptoms. In the active period of the disease, non-specific signs are revealed in the laboratory examination: normochromic anemia, thrombocytosis, neutrophilic leukocytosis and increased ESR, rheumatoid factor, positivity of C-reactive protein. In the clinical analysis of urine: hematuria, erythrocyte cylinders, proteinuria. Along with urinary syndrome, azotemic indicators increase and glomerular filtration rate rapidly decreases.

Keywords Granulomatosis with polyangiitis, Diagnosis, ANCA

1. Introduction

ANCA is a group of immunoglobulin G (IgG) antibodies directed against the cytoplasm of neutrophil granulocytes and monocytes, whose presence in blood serum can be detected by indirect immunofluorescence. Antigens to proteinase 3 (PR3) and myeloperoxidase (MPO) are detected in the PAG. ANCA against these antigens are therefore called PR3-ANCA and MPO-ANCA. Identification of ANCA is important. Immunofluorescence and enzyme immunoassays are widely used to detect ANCA among serological methods. Antibodies specific to proteinase-3 and myeloperoxidase in the presence of neutrophils conjugated with ethanol produce different flashes: they are C-ANCA (cytoplasmic antineutrophil cytoplasmic antibodies) and p-ANCA (perinuclear antineutrophil cytoplasmic antibodies). C-ANCA is mainly associated with sera harboring PR3-ANCA and is specific (>90%) for PAG. C-ANCA has 91% sensitivity and 99% specificity for active GPA [1-7,12]. At the same time, ANCA is an important diagnostic marker of PAG and is not of high value for monitoring the activity of the disease, because they can be in the blood serum during the period of complete clinical remission and may not be detected in the relapse of the disease despite the high activity of vasculitis. Although high activity of ANCA is widespread in the PAG, ANCA may not be the main factor in the development of the disease [8-11,13]. In systemic PAG, ANCA is found in approximately 90% of patienC, and in 80-95% of these patients, antibodies are directed against PR3. C-ANCA has 91% sensitivity and 99% specificity for active GPA.

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2. Purpose

To evaluate the effectiveness of methods of diagnosis of various variants of polyangiitis granulomatosis.

3. Materials and Methods

60 patients with PAG who were treated in inpatient conditions in the rheumatology and cardiorheumatology department of the multidisciplinary clinic of the Tashkent Medical Academy in 2018-2022 and were observed and treated in the outpatient department of the arthrological IATC department were taken as the object of the study.

As the subject of the study, patients' blood serum, x-ray and ultrasound methods, as well as materials for determining the level of disease activity (BVAS) and vasculitis damage index (VDI) were taken.

The research used clinical questionnaire, laboratory analysis, immunological (ANCA), bacteriological inoculation from the nasopharynx, BVAS and VDI indicators, instrumental (MSCT of the nasal cavities and lungs, X-ray examination) and statistical methods.

General examination of patients was carried out according to the plan adopted in the clinic. In studying the anamnesis, special attention was paid to the activity of the disease, damage to various organs and systems.

In the detailed anamnesis study, the premorbid background more than 6 months before the onset of PAG and before the appearance of symptoms of PAG and the conditions that may have caused its development were analyzed. Manifest symptoms of the first month of the disease, clinical manifestations of the exacerbation phase and subsequent relapses were compared.

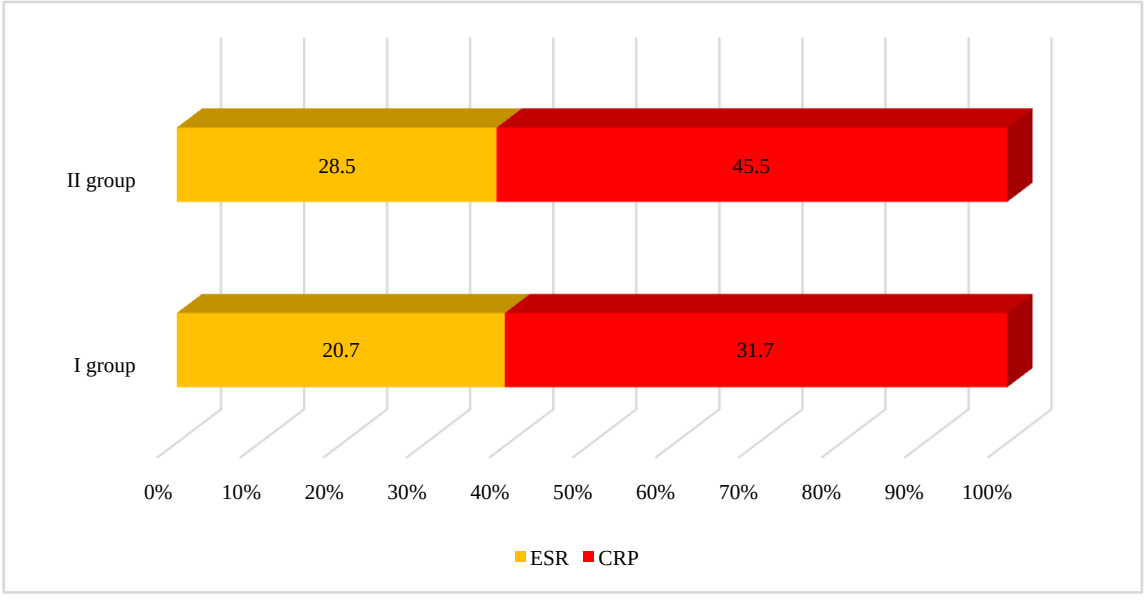
The BVAS scale (Birmingham Vasculitis Activity Index) was used to assess activity. Remission of the disease was considered to have a score of 1 or less on the VVAS scale, PAG exacerbation was considered to be a score of 2 or more on the VVAS scale. Evaluation of organ damage was performed in all patienC using the VDI index. Damage index assessment takes into account damage to organs observed since the onset of vasculitis. Patients often have additional diseases that occurred before the development of vasculitis, which should not be taken into account.

4. Results

ESR and C-reactive protein levels were most elevated in patients with PAG exacerbation compared to patients with PAG remission. The main laboratory indicators are presented in Table 1.

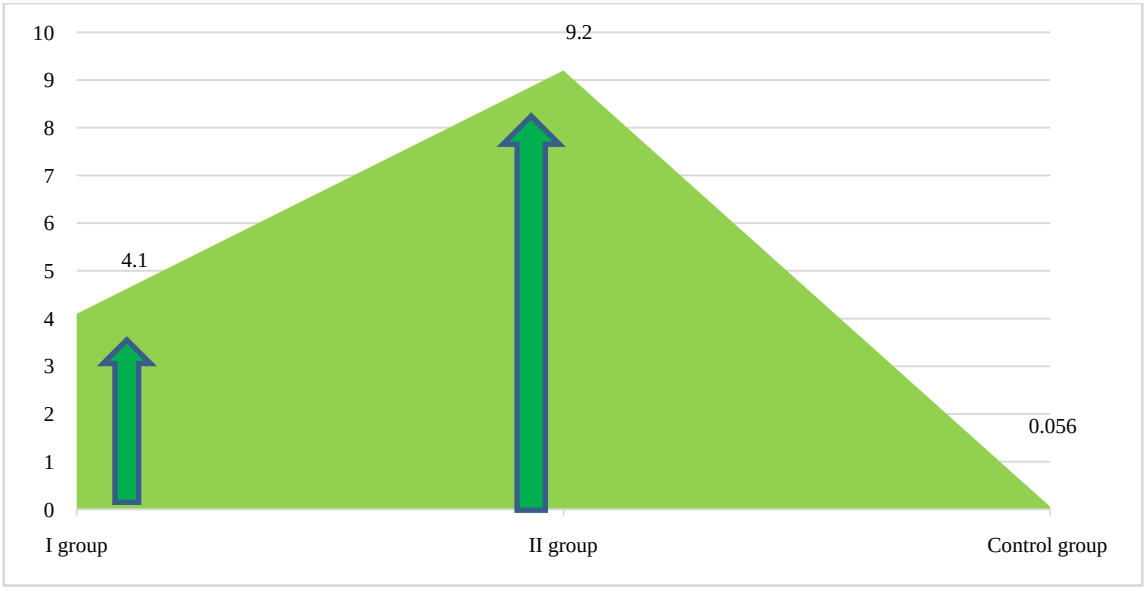
Table 1. Laboratory indicators in patients with PAG according to the form and period of the disease

	General	**Form of the disease**		**Period of the disease**	
	N=60	Local (n=29)	General (n=31)	Adding (n=32)	Remission (n=28)
Ball filtration rate is less than 60ml/min/1.73m2	19 (31.7%)	0	19 (50.0%)	11 (34.4%)	8 (28.6%)
Proteinuria	18 (%)	0	18 (47.4%)	9 (28.%)	9 (28.1%)
Proteinuria more than 0.5 g per day	10 (16.7%)	0	10 (26.3%)	6 (18.8%)	4 (14.3%)
An increase in the amount of creatinine in the blood	16 (26.7%)	0	16 (42.1%)	10 (31.3%)	6 (10.0%)
Average value of creatinine, mg/dl	1.29±1.1	0.91±0.2	1.5±1.3	1.48±1.4	1.08±0.4
Calculation of KFT CKDEPI, ml/min	67.3±28.3	80.1±19.9	59.9±28.2	62.5±28.1	72.7±28.0
Hematuria	12 (20.0%)	0	12 (31.6%)	8 (25.0%)	4 (14.3%)
Average value of daily proteinuria, g/milk	0.21±0.6	0.03±0.1	0.32±0.7	0.26±0.7	0.16±0.3
Increase in ESR	29 (48.3%)	7 (31.8%)	22 (57.9%)	20 (62.5%)	9 (32.1%)
Average value of ESR, mm/s	18.02±16.8	12.23±7.3	21.37±19.8	23.69±20.6	11.54±7.1
Increase of CRP	13 (21.67%)	2 (9.1%)	11 (28.9%)	12 (37.5%)	1 (3.6%)



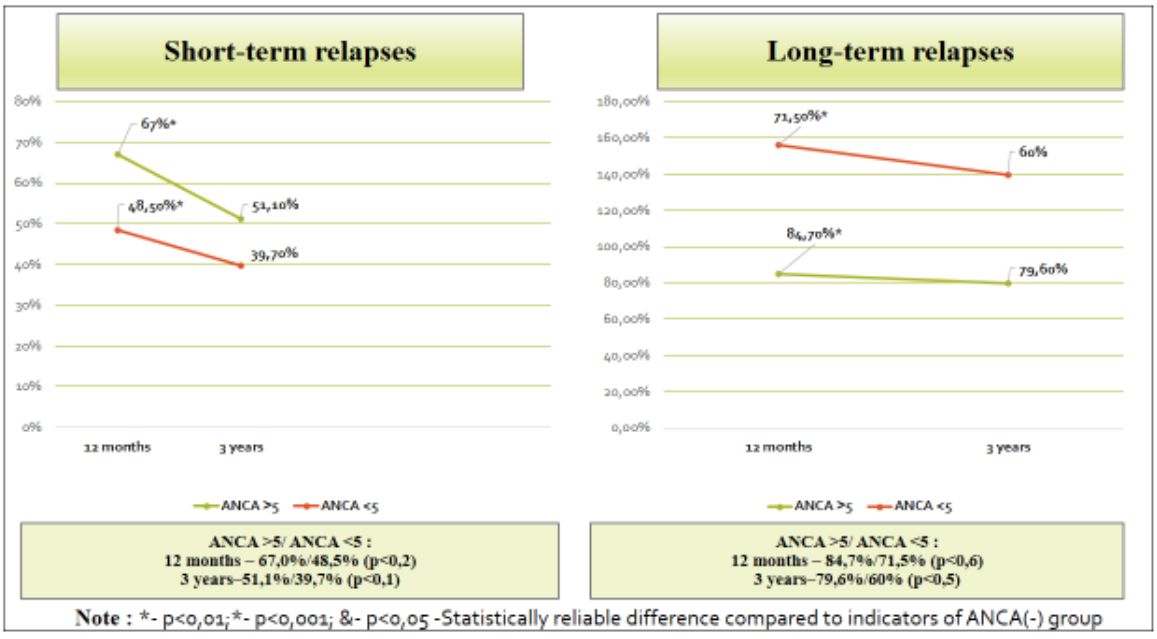
Note - *- p<0,001 -Statistically reliable difference compared to indicators of 1st group

Picture 1. Changes of amounts of ESR and CRP according to the clinical type of PAG



Note - *- p<0,001 -Statistically reliable difference compared to indicators of 1st group
&- p<0,0001 -Statistically reliable difference compared to indicators of control group

Picture 2. ANCA score according to clinical type of PAG



Picture 3. Assessment of disease relapse in patients with PAG by ANCA titer (%)

A decrease in glomerular filtration rate of more than 50% was found in 19 (31.67%) PAG patients with renal vasculitis. 1 (1.7%) patient developed TRGN (increased creatinine from 5 mg/dL to 8.3 mg/dL). In patients with PAG, the urinary syndrome is mainly manifested by hematuria and proteinuria (PU up to 1 g per day - 16 (89.5%), 1-3 g per day - 1 (5.3%), more than 3 g per day (nephrotic syndrome) - 1 (5.3%) was, which was more observed in patients with PAG activation period.

Thus, the expressed stage of PAG is the pathology of the upper respiratory tract, rhinosinusitis (96%) is usually characterized by necrotic/ulcerative necrotic development, hearing organ (41.6%) and larynx (3.3%), foci/infiltrates, the formation of which tends to erode in the lungs (53.3%), may be asymptomatic and GN with hematuria (38.3%), fever and arthralgia/arthritis in every third case (13.3%). Fewer skin damage (8.3%), eyes (41.6%), cardiovascular pathology (3.3%).

In the diffuse type of PAG, i.e., in the 2nd group, significantly higher indicators of CRP and ESR were also distinguished (pic. 1).

ANCA was detected in 58 (93.3%) patients, 2 (3.3%) patients remained ANCA-negative throughout the follow-up period. Antibodies to PR-3 were detected more often in 48

(80%) than to MPO antibodies in 10 (16.6%) patients, women predominated in both groups 11 and 19, respectively.

The titer of antineutrophil cytoplasmic antibodies, ANCA, which is an immunological marker of PAG, was significantly lower in the local type than in the diffuse type (pic. 2).

According to statistics, a high titer of ANCA indicates more damage to internal organs. Our scientific study confirmed this conclusion, showing a higher frequency of organ damage in PAG patients with ANCA titer higher than 5. (Table 2).

Table 2. Assessment of the association of clinical and laboratory indicators of the disease with ANCA titer in patients with PAG (n=60)

Clinic-laboratory indicators	ANCA (<5) (n=21)	ANCA (>5) (n=39)
Arthralgia	13 (61,9%)	35 (89,7%)*
An increase in body temperature	18 (85,7%)	37 (94,8%)*
Damage to the nose and nasal cavities	14 (66,6%)	29 (74,3%)*
Damage to organs of vision	5 (23,8%)	13 (33,3%)*
Kidney damage	1 (2,1%)	24 (61,5%)**
Damage to the lungs	2 (4,2%)	18 (46,1%)**
BVAS	21,4±0,5	28±7,5 &
VDI	0,4±4,5	0,9±4,5&
ESR	26±8,6	38±6,2*
CRP	24,6±4,3	31,5±9,1*

Note - *- p<0,01;*- p<0,001; &- p<0,05 -Statistically reliable difference compared to indicators of ANCA(-) group

No significant difference was found in the titer of ANCA in the course of PAG. The frequency of short-term and long-term recurrences did not differ significantly between the two disease types. However, PAG with higher ANCA titer had higher clinical severity of relapses (pic. 3).

In the group of patients with AT to PR-3, the frequency of damage to the organs of vision (r=0.05) and the presence of the area of consolidation in the lungs at the end of the follow-up (r=0.009) were found to be much higher than in the group of patients with AT to MPO. At the same time, patients with PR-3 -ANCA had higher creatinine level at the first onset of the disease (r=0.025). Lung, kidney, and other organ damage were not significantly different. There were also no significant differences in mortality, attack frequency, activity scores, and injury nonreversibility. During relapse, the level of ANCA may exceed the values determined at the beginning of the disease. Of particular interest is the ANCA-negative variant of the PAG. In this sample, 2 patients with ANCA-negative status were identified, among them 1 woman, 1 man, the average age was 49.4 years, the follow-up period was 20.5 months. There were no differences in the values of BVAS and VDI indices when compared. These patients had severe clinical manifestations of PAG, therefore, 1 patient developed diffuse alveolar hemorrhage, 1 patient was noted to have increased renal function to stage 3B and higher at the end of follow-up.

The conclusion allows us to conclude that patients with high titers of ANCA and CRP in the early diagnosis and exacerbation of PAG have a high frequency of damage to internal organs and, at the same time, are predictors of severe consequences.

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