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Evaluation of the efficiency of methods of diagnostics of various variants of granulomatosis with polyangiitis

Berdieva D.U.
Tashkent Medical Academy, Uzbekistan

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Abstract: Early diagnosis of granulomatosis with polyangiitis (GPA) is a difficult clinical task and requires a thorough examination of the patient using modern research methods to identify pathognomonic symptoms. It is necessary to specifically search for respiratory tract damage by performing rhinoscopy, laryngoscopy, computer tomography of the paranasal sinuses, and lung scans, as the disease may be asymptomatic or have minimal clinical symptoms for a long time. Only 50% of patients are diagnosed within the first 3-6 months of disease onset, while in 7%, GPA remains undetected for 5-16 years after the first symptoms appear.

In the active period of the disease, non-specific signs are revealed in the laboratory examination: normochromic anemia, thrombocytosis, neutrophilic leukocytosis and an increase in ESR, rheumatoid factor, positivity of C-reactive protein. Clinical analysis of urine: hematuria, erythrocyte casts, proteinuria. Along with the urinary syndrome, azotemic indicators increase and the glomerular filtration rate decreases rapidly.

Keywords: Granulomatosis with polyangiitis, diagnosis, ANCA.

Introduction: ANCA is a group of immunoglobulin G (IgG) antibodies directed against the cytoplasm of neutrophil granulocytes and monocytes, the presence of which in blood serum can be detected indirectly by immunofluorescence. In PAG, antigens are detected for proteinase 3 (PR3) and myeloperoxidase (MPO). ANCA against these antigens is therefore called PR3-ANCA and MPO-ANCA. The detection of ANCA is important. Among serological methods for the detection of ANCA, immunofluorescence and enzyme-linked immunosorbent assays are widely used. In indirect immunofluorescence in the presence of ethanol-fixed neutrophils, antibodies specific for proteinase-3 and myeloperoxidase produce different fluorescences: they are c-ANCA (cytoplasmic antineutrophil cytoplasmic antibodies) and p-ANCA (perinuclear antineutrophil cytoplasmic antibodies). c-ANCA is mainly associated with serum containing PR3-ANCA and is specific for PAH (>90%). c-ANCA has a sensitivity of 91% and specificity of 99% for active HPA [1-7]. However, ANCA is an important diagnostic marker of PAH and has a low value for monitoring disease activity, because they can be present in the serum during complete clinical remission and may not be detected in relapses despite high vasculitis activity. Although high ANCA activity is common in GPA, ANCA is unlikely to be a major factor in the development of the disease [8-11]. In systemic GPA, c-ANCA is found in approximately 90% of patients, and in 80-95% of these patients, antibodies are directed against PR3. c-ANCA has a sensitivity of 91% and specificity of 99% for active GPA.

Purpose: To evaluate the effectiveness of methods of diagnosis of various variants of polyangiitis granulomatosis

METHODS

The study subjects were 60 patients with GPA who were treated inpatiently in the rheumatology and cardiorheumatology departments of the Multidisciplinary Clinic of the Tashkent Medical Academy in 2018-2022 and who were monitored and treated on an outpatient basis in the arthrological IADC department.

The subjects of the study included patients' blood serum, radiological and ultrasound examination methods, as well as materials for determining the level

of disease activity (BVAS) and determining the vasculitis damage index (VDI).

The study used a clinical questionnaire, laboratory tests, immunological (ANCA), nasopharyngeal bacteriological culture, BVAS and VDI indicators, instrumental (paranasal sinus and lung CT, X-ray examination) and statistical methods.

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

In the detailed anamnesis study, the premorbid background more than 6 months before the onset of GPA and the conditions that preceded the appearance of GPA symptoms and could cause 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 (Bermingham Vasculitis Activity Index) was used to assess activity. Remission of the disease was considered to be a BVAS score of 1 or less, and exacerbation of GPA was considered to be a BVAS score of 2 or more. Organ damage was assessed in all patients using the VDI index. The damage index takes into account the organ damage observed since the onset of vasculitis. Patients often have additional diseases that arose before the development of vasculitis, which should not be taken into account.

RESULTS

Patients with exacerbation of GPA had significantly higher erythrocyte sedimentation rate and C-reactive protein levels compared with patients in remission of GPA. The main laboratory parameters are presented in Table 1.

TABLE 1

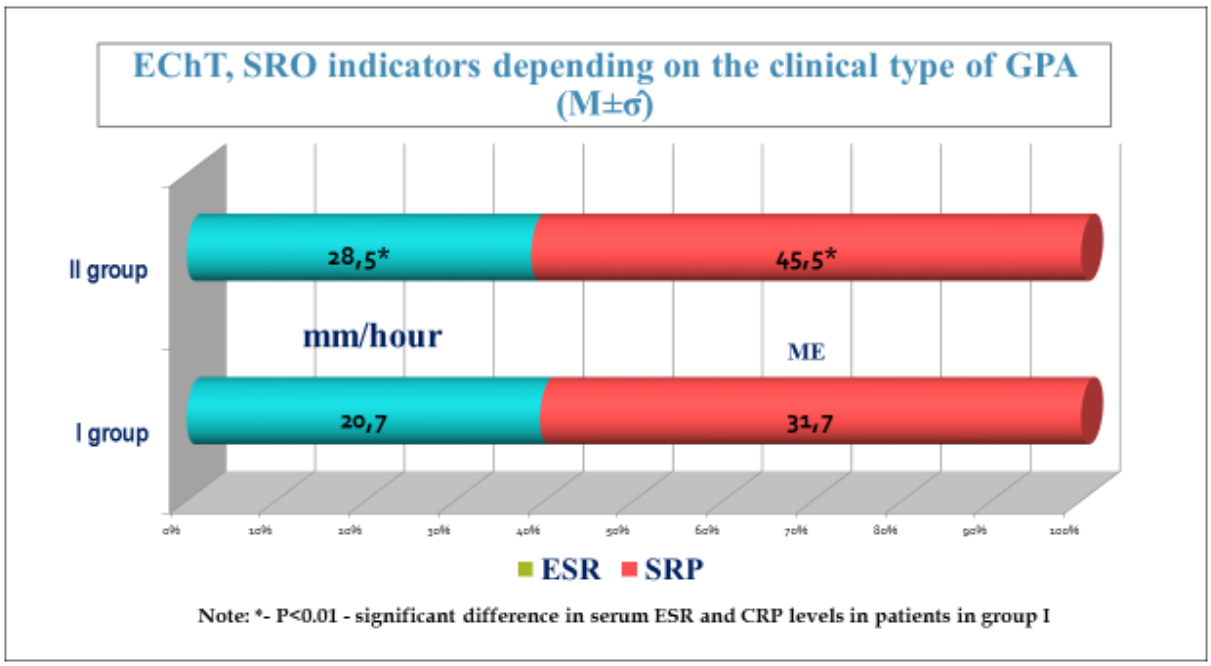
Laboratory indicators in patients with PAG according to the form and period of the disease

	General	Disease form		Disease period	
	N=60	Local (n=29)	Generalized (n=31)	Intensification (n=32)	Remission (n=28)
Glomerular filtration rate less than 60 ml/min/1.73 m2	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/day	10 (16.7%)	0	10 (26.3%)	6 (18.8%)	4 (14.3%)
Elevated creatinine levels in blood	16 (26.7%)	0	16 (42.1%)	10 (31.3%)	6 (10.0%)
Mean 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
GFR reading 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 daily	0.21±0.6	0.03±0.1	0.32±0.7	0.26±0.7	0.16±0.3

proteinuria, g/day					
Elevated ESR	29 (48.3%)	7 (31.8%)	22 (57.9%)	20 (62.5%)	9 (32.1%)
Average ESR value, mm/s	18.02±16.8	12.23±7.3	21.37±19.8	23.69±20.6	11.54±7.1
Increased CRP	13 (21.67%)	2 (9.1%)	11 (28.9%)	12 (37.5%)	1 (3.6%)

A decrease in glomerular filtration rate of more than 50% was found in 19 (31.67%) GPA patients with renal vasculitis. TRGN development was noted in 1 (1.7%) patient (increased creatinine from 5 mg/dL to 8.3 mg/dL). In patients with PAG, urinary syndrome was 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%), which was observed more often in patients with an exacerbation of GPA.

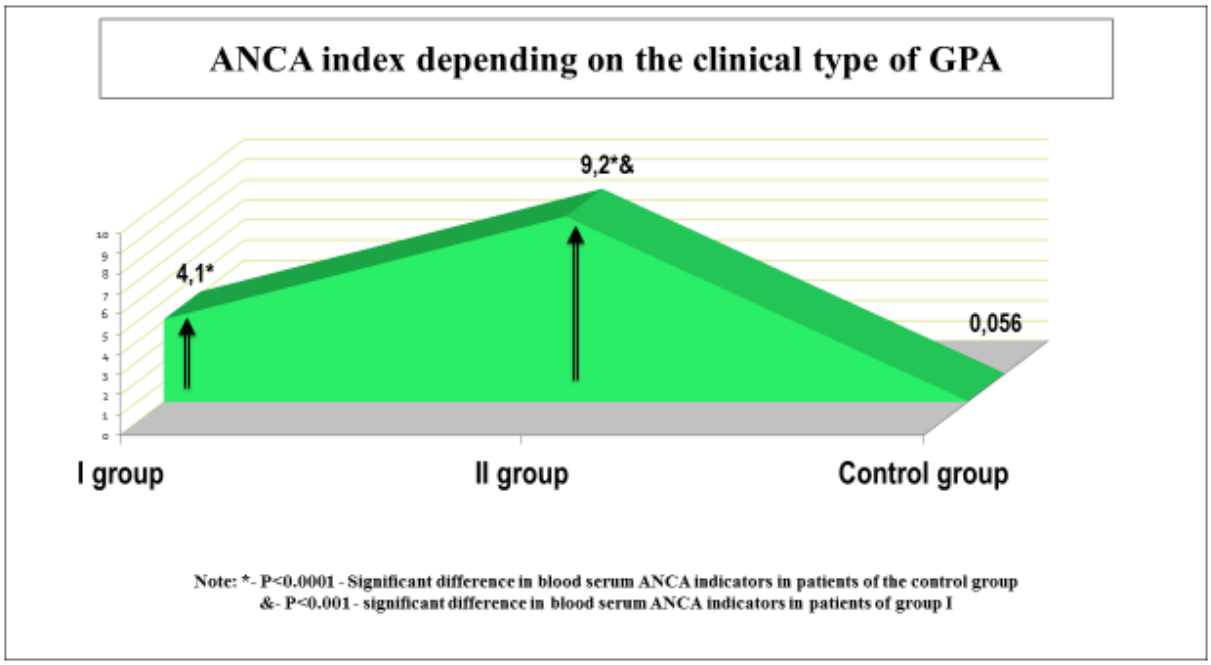
Thus, the expressed stage of GPA is characterized by the development of upper respiratory tract pathology, usually with necrotic/ulcerative involvement of rhinosinusitis (96%), the organ of hearing (41.6%) and the larynx (3.3%), the formation of foci/infiltrates prone to resorption in the lungs (53.3%), can be asymptomatic and develop GN with hematuria (38.3%), fever and arthralgia/arthritis in every third case (13.3%). Less skin lesions (8.3%), eyes (41.6%), cardiovascular pathology (3.3%). In the diffuse type of GPA, i.e., group 2, significantly higher indicators of CRP and ESR were also distinguished (Fig. 1).



Note: *- P<0.01 - significant difference in serum ESR and CRP levels in patients in group I

ANCA was detected in 58 (93.3%) patients, 2 (3.3%) patients remained ANCA-negative throughout the entire follow-up period. Antibodies to PR-3 were detected in 48 (80%) patients, more often than anti-MPO antibodies, with a female predominance in both groups (11 and 19, respectively).

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



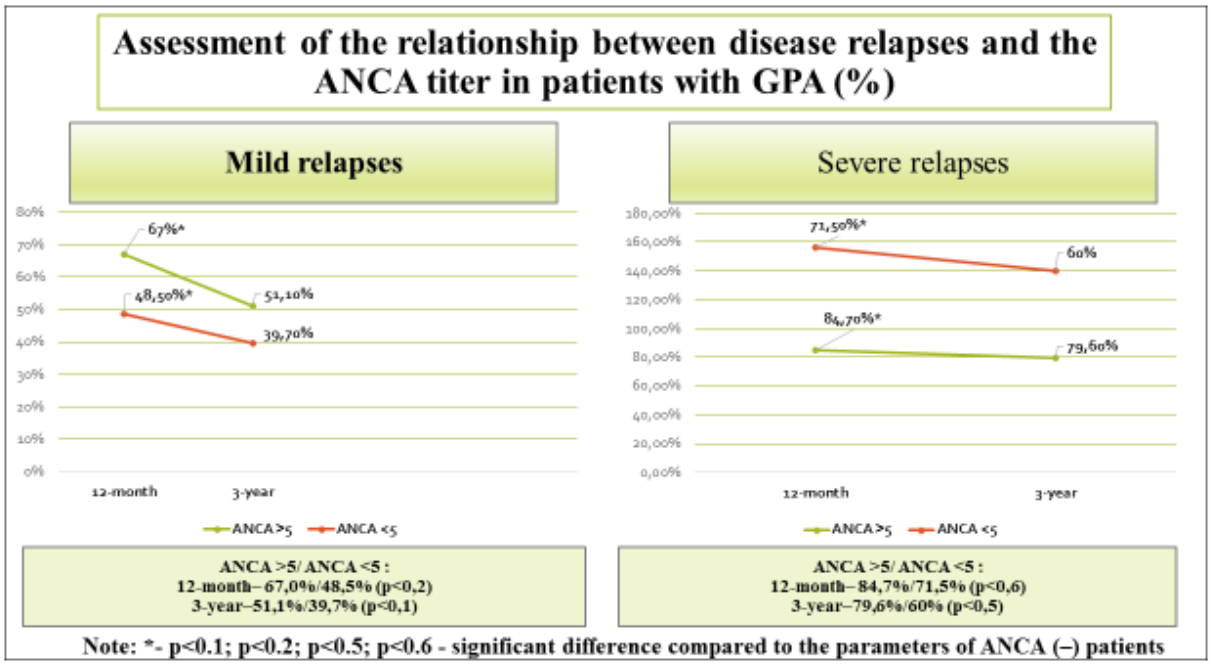
According to statistical data, a high titer of ANCA indicates more damage to internal organs. Our scientific study confirmed this conclusion, showing a higher frequency of organ damage in GPA patients with ANCA titer higher than 5. (Table 2)

Assessment of the relationship of clinical and laboratory parameters of the disease with the ANCA titer in patients with GPA (n=60)

Clinical and laboratory indicators	ANCA (<5) (n=21)	ANCA (>5) (n=39)
Arthralgia	9 (42,8%)	24 (61,5%)*
Body temperature rise	13 (61,9%)	35 (89,7%)*
Injury of nose and paranasal sinuses	18 (85,7%)	37 (94,8%)*
Injury of organs of vision	14 (66,6%)	29 (74,3%)*
Injury of hearing organs	5 (23,8%)	13 (33,3%)*
Lung involvement	1 (2,1%)	24 (61,5%)**
Kidney damage	2 (4,2%)	18 (46,1%)**
BVAS	21,4±0,5	28±7,5 &
VDI	0,4±4,5	0,9±4,5&
SRP	26±8,6	38±6,2*
ESR	24,6±4,3	31,5±9,1*

Note: *- p<0.01; ** - p<0.001; &- p<0.05-significant difference in relation to the indicators of patients with ANCA (-)

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



In the group of patients with PR-3-AT, the frequency of visual organ damage (p=0.05) and the presence of

areas of consolidation in the lungs at the end of follow-up (p=0.009) were significantly higher than in the group of patients with MPO-AT. At the same time, patients with PR-3-ANCA had higher creatinine levels at the initial onset of the disease (p=0.025). There was no significant difference in lung, kidney, or other organ damage. There were also no significant differences in mortality, seizure frequency, activity parameters, or nonreversibility of lesions.

During the recurring period, ANCA levels may exceed those detected at the onset of the disease. Of particular interest is the ANCA-negative variant of GPA. In this sample, 2 patients with ANCA-negative status were identified, 1 female, 1 male, mean age 49.4 years, and follow-up period 20.5 months. There were no differences in the values of BVAS and VDI indices when compared. These patients had severe clinical manifestations of GPA, as a result of which diffuse alveolar hemorrhage developed in 1 patient, and in 1 patient, renal function increased to stage 3B and higher at the end of observation.

CONCLUSION

Early diagnosis and exacerbation of GPA allow us to conclude that patients with high serum ANCA and CRP titers have a higher incidence of internal organ damage and, at the same time, are predictors of severe outcomes.

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