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Clinical-Neurophysiologic, Immunological Features And Diagnosis Of Antifosfolipid Syndrome By Cerebra-Vascular Disorders At Background Systemic Diseases Of Connective Tissue

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Abstract: Antiphospholipid Syndrome (AFS) is one of the current multidisciplinary problems of modern medicine and is being investigated as a unique example of autoimmune thrombotic vasculopathy. This syndrome was first described in the context of Systemic lupus erythematosus (TSA) and was referred to as anticardiolipin syndrome, later renamed antiphospholipid syndrome (AFS) by the same authors. There is an immunological predisposition to increased synthesis of antiphospholipid antibodies (AFL) and most of them have been detected in relatives of patients with AFS.

The prevalence of AFS in the population is still unknown. It is possible that the synthesis of antiphospholipid antibodies (AFL) may be normal, but often low levels of antibodies are observed in the blood of a healthy person. According to various data, the rate of antibody cardiolipin (ACL) in the population varies from 0 to 14%, averaging 2-4%, with high titers detected in about 0.2% of donors.1 In Uzbekistan, systemic connective tissue is found in several people per year. The disease develops antibodies to the interaction with phospholipids - components of the cell membrane.

Keywords: AFS(Antiphospholipid Syndrome), UTTKDG, systemic lupus erythematosus (TQB),systemic scleroderma (TSD), nervous system, normal activity of beta-2-glycoprotein (B2GPI).

Nervous system injury includes transient ischemic attack, ischemic stroke, chronic cerebral ischemia, epilepsy, migraine, chorea, myelitis, neurosensory hearing loss, and other neurological and psychiatric symptoms that are very severe (fatal) manifestations of AFS. Various neurological manifestations in AFS are mainly related to the localization of the vascular injury and its degree of expression, which may lead to a lack of vision or disability. In AFS, there is evidence that damage to the nervous system is partially latent in nature, occurs gradually during clinical manifestation, and is incurable. Sometimes cerebral ischemia is associated with thromboembolism, which is the source of the internal carotid artery or heart cavity and valves. The incidence of ischemic stroke is higher in patients with heart valve (mainly left ventricular) injury.

It has a serious impact on disability and mortality rates due to cerebrovascular disorders. Therefore, the development of methods for determining and diagnosing the role of AFS in the origin of cerebrovascular disorders and its application in medical practice is one of the important medical and social issues. Along with the work on the diagnosis, prevention and modern treatment of AFS in Uzbekistan, there is a need to expand the possibilities of early detection of AFS in systemic diseases of clinical connective tissue and prevention of possible complications in neurology. As a result, the population will have the opportunity to provide highly qualified medical care that meets today's requirements.

Important tasks have been set in the country to improve the social protection and health care system, prevent common diseases and introduce advanced, tested methods of early detection, improve the quality of medical care, provide them with specialized and high-tech medical care. Therefore, strengthening the health of the population, in particular, the role of antiphospholipid syndrome in the development of cerebrovascular insufficiency in systemic connective tissue diseases, reducing the risk factors, providing specialized medical care to patients, further development and improvement of effective treatment, reducing and prolonging life expectancy is one of the important areas of medicine. In accordance with the Action Strategy for the five priority areas of development of the Republic of Uzbekistan in 2017-2021, it is important to raise the level of medical services to a new level, aimed at "... prevention and diagnosis of diseases, widespread introduction of modern technologies, high quality and quality care." practical work is defined. In the implementation of these tasks, one of the urgent issues is the development of a set of early diagnosis, prevention and subsequent rehabilitation of antiphospholipid syndrome in cerebrovascular disorders in systemic diseases of connective tissue.

For comparison, 40 patients with essential arterial hypertension and simultaneous central arterial atherosclerosis of the head and arterial hypertension were obtained, which corresponded to the age-sex composition without diseases of the rheumatic profile.

All patients were examined and treated at the Department of Rheumatology of the Department of Internal Medicine Propaedeutics and Regional Multidisciplinary Central Hospital of the ADTI Clinic, and then under the supervision of the dispensary for many years.

The reliability of the diagnosis in patients with TQB was determined on the basis of ARA criteria, patients with less than 4 criteria were excluded from the study. The diagnosis of TSD was considered reliable when the criteria recommended by ARA experts were available. The group of systemic vasculitis included all cases of hemorrhagic capillary disorders, including adult patients without other causes for the development of vasculitis, as well as Shenlein-Genoxpurpuris.

Most patients underwent re-examination (2–10 times), with a follow-up period of 2 months to one year. The total number of follow-ups was 142.

Of those surveyed, 129 (85.5%) were women and 37 (14.5%) were men. Women predominated in TB, TSD, TV, and other forms of the disease (94.3%, 100%, 100%).

The mean age of patients was 39 ± 12.7 years, the age of patients with rheumatoid arthritis was the highest (48.5 ± 7.8 years), while the age of patients with systemic lupus erythematosus was the youngest (33.7 ± 11.3 years). observed. The overall rheumatic process in the group led for an average of 31.1 ± 11.2 years.

Magnetic resonance imaging (MRI) of the brain is performed on a MAGNETOMOPEN SIMENS device for visual assessment of the state of the brain substance at a magnitude of 0.5 T magnetic induction by standard method (T1 and T2 order, sagittal, axial and frontal cross-sectional density, 1-10 mm cross-sectional thickness) increased. Brain MRI was performed in 187 patients with systemic connective tissue disease.

A commercial kit developed by ORGENTEC Diagnostics (Germany) for IFA was used to determine the total amount of IgG / IgM anti-cardiolipin and IgG / IgM anti-beta-2-glycoproteins in patients 'serum.

In order to check the clinical, biochemical parameters of peripheral blood, the indicators (leukocyte, erythrocyte, hemoglobin, total protein and fraction, ECG) and the state of blood clotting time were determined in the comparison group and patients with various forms of systemic diseases of connective tissue.

A standardized card was completed for each patient. Statistical processing was carried out using data generated on the basis of all programs on a personal computer, which included the results of clinical, laboratory and instrumental methods of testing.

In our control were 35 patients with TB from the first months of disease development (7 patients 6.7%) to 17 years. The main symptom of the disease was detected in 23 patients. Most often it was observed in the form of "vascular butterfly" (30.6%), polyarthritis (28.2%) and fever (16.5%). Acute cerebrovascular accident (CBD) was reported as the first manifest sign of the disease in 12.9% of cases.

Clinically manifested polymorphism is specific for TQB patients, in which several leading factors can be combined (Table 1). The most common clinical manifestations were various skin symptoms: trophic disorder in 77.4% of patients, retinal detachment in 32% of patients, polyarthritis and vascular syndrome of polyarthralgia type (77.4%). Among visceral injuries, renal injury (58.8%) ranked first, while lupus nephritis was detected in 92.2% of these patients. Generalized lymphadenopathy observed in 40.6% of TQB patients reported retraction of the reticuloendothelial system. The main clinical signs were given in TQB patients.

Our study examined 39 patients with various forms of systemic connective tissue disease based on the presence of IgG / IgM class antibodies to cardiolipin: 19 patients with systemic lupus erythematosus (TSA), 11 patients with systemic scleroderma (TSD), and 9 patients with rheumatoid arthritis (RA).

The results of the detection of IgG / IgM class antibodies to cardiolipin are given in Table 3.1.

The results showed that in patients diagnosed with systemic lupus erythematosus, both IgG / Ig M class antibody levels tested for cardiolipin were significantly increased. In groups 2-3, patients were diagnosed with systemic scleroderma and rheumatoid arthritis, IgG anti-cardiolipin levels differed from control group reference values, and IgM class antibody concentrations were significant, 3 times higher than analogues of healthy individuals. This is shown in Table (1).

The results obtained show the appearance of dynamic changes in the concentration of autoantibodies associated with the development of systemic diseases of connective tissue. In many patients, disease duration leads to stagnation of IgG class autoantibody levels within the reference summary (except in patients with systemic lupus erythematosus), induces

synthesis of IgM class autoantibodies, such as exacerbation of the pathological process, indicating a significant increase in this autoantibody concentration in cardiolipin.

Table 1

Detection of IgG / IgM class antibodies to cardiolipin in patients with systemic connective tissue disease

Groups	**Anti-cardiolipin, U / ml**	
	IgG	**IgM**
Group 1 - systemic lupus erythematosus (TQB), n = 19	15,17±0,58*	60,5±2,47*,**
Group 2 - systemic scleroderma (TSD), n = 11	8,29±0,12	33,86±1,04*,**
Group 3 - rheumatoid arthritis (RA), n = 9	10,35±0,25	36,59±2,19*,**
Control (healthy people) #	10,0	10,0

* - p <0.05 (comparison with the control group);

** - p <0.05 (comparison with analog indicators for IgG antibody class); # - TQB diagnosis The IgM antibody class index was 6 times higher than the reference sum according to the average reference sum in the instruction set for IFA.

It should be noted that the presence of a phospholipid-directed antiphospholipid antibody that binds to plasma proteins such as beta-2-glycoprotein I (b2GPI) or anti-cardiolipin is a hallmark of the development of primary or secondary antiphospholipid syndrome and systemic lupus erythematosus or other conditions (e.g. directly related to autoimmune disorders such as. Successful diagnosis of the syndrome requires a combination of at least one clinical and one laboratory criterion for antiphospholipid antibody manifestation persistence (i.e., volcanic anticoagulants, cardiolipin, and / or IgG versus IgG or IgM or IgM against b2GPI) for at least 12 months. Classification criteria were adopted at the 8th International Congress on APL in 2000, which was reviewed in 2006 (criteria for antiphospholipid syndrome classification in Sapporo) and adopted by the British Committee on Hematology Standards for Diagnosis in 2012 as Thrombotic and Obstetric Syndrome (BCSH) .Thrombocytopenia, autoimmune hemolytic anemia, heart valve disease caused by Coombs syndrome, renal microangiopathy, chorea, and longitudinal myelitis are also common in patients with anticardiolipin-positive but not included in the classification criteria (so-called “non-criteria”)

Thus, the results obtained have diagnostic value in differential diagnosis and treatment monitoring in patients with systemic connective tissue diseases.

An increase in the detected amount of anticardiolipin in the peripheral blood of patients with systemic lupus erythematosus belonging to classes IgG and IgM, along with the clinical manifestations of this pathology may be information about the development of the disease and activation of the body's autoimmune response after previous treatment.

Examination of the amount of anti-cardiolipins in the peripheral blood of patients with systemic scleroderma revealed that IgM class autoantibodies serve as a marker of the pathological process, ie in this pathology the autoimmune process is "acute" and can be

diagnosed in a relatively short time (2-4 weeks). This can complicate the laboratory diagnosis of systemic scleroderma in a practical health setting and requires the establishment of a set of biomarkers to reliably detect the onset of the pathological process and successfully monitor the treatment performed, i.e. to determine the diagnostic phenotype of the disease.

In determining the amount of anti-cardiolipins in the peripheral blood of patients with rheumatoid arthritis, again in the case of systemic scleroderma, IgG class autoantibodies were not considered a reliable biomarker in the pathological condition, while IgM class autoantibodies were significantly higher than the reference sum. In this disease, the autoimmune process is "acute" and can be diagnosed in a relatively short time (up to 2-4 weeks).

Studies in patients diagnosed with connective tissue systemic diseases in the presence of anti-cardiolipin have shown dynamic changes in the amount and class of antibody detected, depending on the pathological etiology and course of the disease. This requires the identification of a diagnostic phenotype specific to connective tissue systemic diseases.

The normal activity of beta-2-glycoprotein (B2GPI) is determined by a rigorous study of its complex protein structure. B2GPI contains five repeating domains in approximately 60 amino acid regions, which is analogous to the super family of other control protein complement. The 5-domain expands to the S-terminus and the additional disulfide bond, which provides a positive charge leading to the approach of the anionic phospholipid. The crystal structure of B2GPI was first identified in the late 1990s and It looks like the letter J »or a hockey stick. Recent studies using electron microscopy have shown that the structure of B2GPI does not limit a single conformation. In general, B2GPI can adopt a different geometry in the liquid phase, possibly due to its ability to change in its interaction with the autoantibody. B2GPI has a round shape in the blood plasma, with domains 1 and 5 opposite each other. In this form, the site that connects the autoantibody is screened. The membrane-bound B2GPI binding of anti-B2GPI stabilizes the J-quality structure and enhances B2GPI interaction with membrane phospholipids, patenting B2GPI signal transmission through other transmembrane and intracellular ligands. It includes plate-like receptors: TLR2 and TLR4, annexin A2 and LRP8. Signaling through these molecules mediates the prothrombotic cellular effect. We examined 39 patients with various forms of systemic connective tissue disease for beta-2-glycoprotein (B2GPI) IgG / IgM class antibody: systemic lupus erythematosus (TQB) - 19.

Table 2

Detection of beta-2-glycoprotein (B2GPI) IgG / IgM class antibody in patients with systemic connective tissue disease

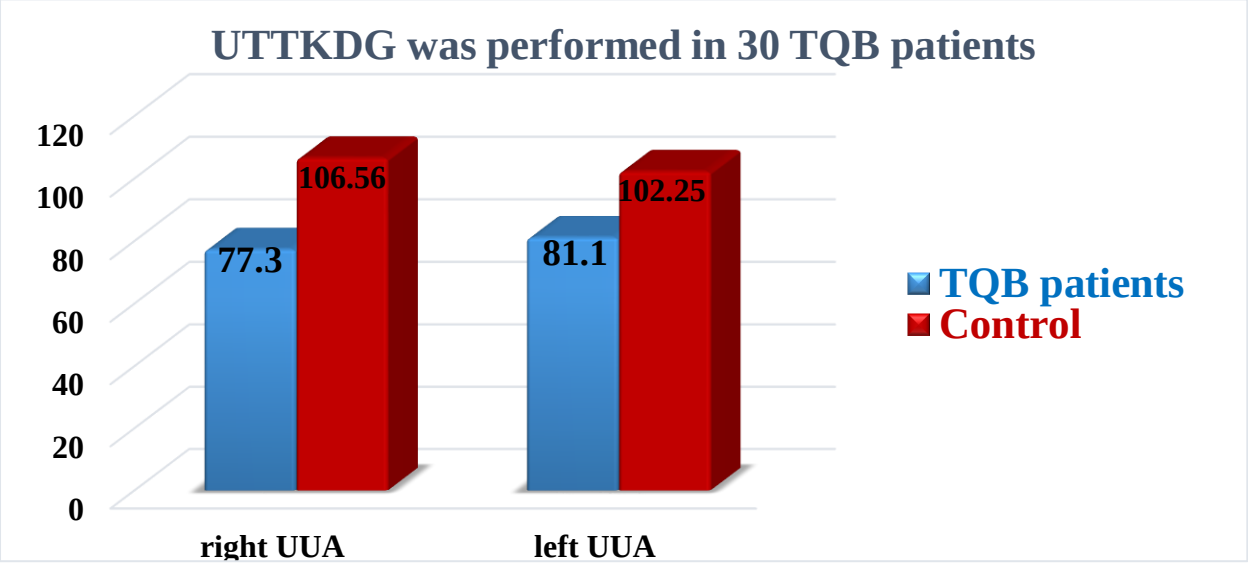
Groups	**beta-2-glycoprotein (B2GPI), U / ml**	
	IgG	**IgM**
Group 1 - systemic lupus erythematosus (TQB), n = 19	17,83±1,44	35,94±1,86*,**
Group 2 - systemic scleroderma (TSD), n = 11	6,29±0,28*	13,14±0,35*,**
Group 3 - rheumatoid arthritis (RA), n = 9	7,71±0,19*	21,82±1,62**
Control (healthy people) #	20,0	20,0

* - p <0.05 (comparison with the control group);
** - p <0.05 (by comparison of analogous indicators for IgG antibody class);
# - data were provided according to the mean reference sum shown in the kit recommendations for rheumatoid arthritis (RA) -9 individuals, systemic scleroderma (TSD) - 11 individuals, IFA per person.

Status of brain dynamics in TQB patients

UTTKDG was performed in 30 TQB patients. According to the UTTKDG, the linear velocity of blood flow along the right common carotid artery (UCAA) was 77.3 ± 15.6 cm / s, and along the left common carotid artery (CUUA) - 81.1 ± 18.7 cm / s in patients with TQB. and was reliably (r <0.01) lower than the comparison group (106.56 ± 6.53 cm / s and 102.25 ± 4.203 cm / s).

Diagram 1



The linear velocity of blood flow through the right internal carotid artery (OIUA) was 74.7 ± 7.9 cm / s and was reliably low compared to the comparison group (80.3 ± 4.3 cm / s), while the left internal carotid artery at TQB on the artery (ChIUA) - was 73.9 ± 11.2 cm / s. The linear velocity of blood flow along the right midbrain artery (UCA) was 88.3 ± 22.1 cm / s, and on the left midbrain artery (UCA) - 100.7 ± 32.3 cm / s. The linear velocity of blood flow in the right vertebral artery (UVA) was 26.2 ± 7.2 cm / s, in the left vertebral artery (CHUA) in TQB - 26.8 ± 8.3 cm / s, the linear velocity of both blood vessels was compared. relative to the group (52.2 ± 14.8 cm / s and 54.4 ± 18.7 cm / s) was reliably low (r <0.01). In TQB patients, the velocity of blood flow (linear) through the main artery (AA) was 47.0 ± 6.5 cm / s. In all cases, blood flow was central in the spinal arteries and was symmetrical in 87.5% of cases and symmetrical in 12.5% of cases (Fig. 1).

Against the background of minimal activity of the pathological process on MRI of 9 patients in 55.6% (5 people) subarachnoid space, in 33.3% (3 people) moderate expansion of the ventricular system, in 13.3% (2 people) foci in the subcortical ganglia, cortical foci in 11.1% (1 person), periventricular foci in 13.3% (2 people), foci of “new” foci in 20% of patients in this group, and thickening of the cerebral cortex in 3 patients (33.3%).

At an average level of activity among 12 patients, 16.7% (2 people) had subarachnoid space dilatation, 25% (3 people) had ventricular enlargement, 8.3% (1 person) had multiple foci in the basal ganglia, and 8.3% had (1 person) cortical foci, in 16.7% (2 people) periventricular foci, in half of patients "new" foci, in 4.3% of cases the cerebral cortex was thickened.

Among 14 patients with active levels, 57.1% (8 people) had subarachnoid space dilatation, 42.8% (6 people) had ventricular dilatation, 7.1% (1 person) had cortical foci, and 14.2% had (2 people) periventricular foci, “new” foci in half of patients, thickening of the cerebral cortex in 1 patient (7.1%).

Patients with minimal activity differed from patients with moderate activity with frequent enlargement of the subarachnoid space ($r < 0.01$) and thickening of the cerebral cortex ($r < 0.01$). Patients with minimal activity differed from patients with high activity with frequent focal lesions of the cortical ganglia ($r < 0.01$) and very rare occurrence of “new” foci ($r < 0.01$). Patients with moderate activity were distinguished from high-activity patients by the presence of frequent focal lesions of the cortical ganglia ($r < 0.01$) and the presence of periventicular foci up to 5 mm relative to 5-10 mm foci of fully expressed activity ($r < 0.01$).

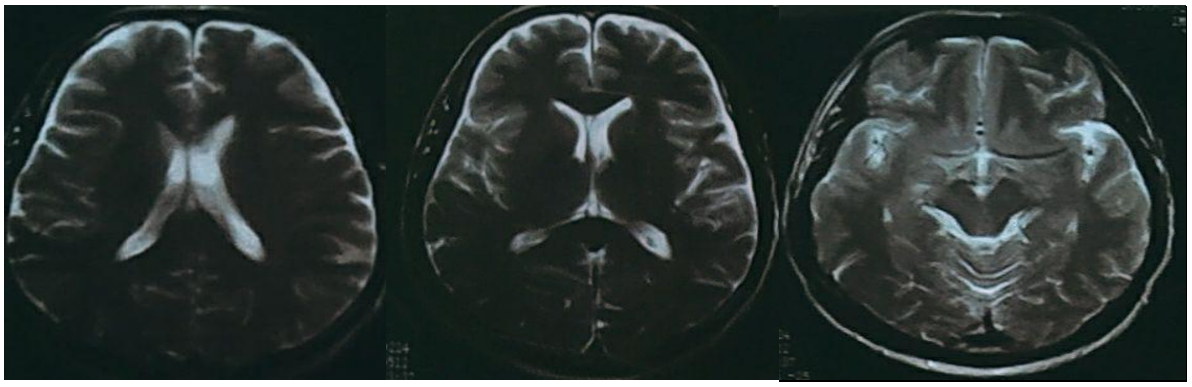


Figure 1. MRI changes in examined patients.

Thus, in “moderate” and fully expressed activity, “new” periventicular foci often occur; furnaces of larger size in expressed activity; At minimal activity - signs of cerebral atrophy with subcortical foci, signs of thickening of the cerebral cortex and enlargement of the subarachnoid space

AFS is one of the neurological manifestations of systemic diseases of the connective tissue, lasting a long time and leading to severe disorders in the nervous system. AFS criteria are determined by the patient's age, recurrence of neurological disorders, the presence of focal lesions of the white matter of the brain according to MRI data.

Among patients with neurological disorders and systemic connective tissue disease, the clinical diagnosis of AFS is primarily systemic AFS (thrombosis, fetal infertility, cytopenia, livedo) and thrombosis (early manifestation of cerebrovascular insufficiency, various stages of cerebrovascular encephalopathy) acute circulatory disorders) is based on the neurological manifestations of AFS, as well as the presence of "rheumatic manifestations" (arthralgia, pain in the spine).

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