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Clinical and Immunological Parallels of Non-Ischemic Damage to The Nervous System in Pregnant Women with Antiphospholipid Syndrome

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ABSTRACT

Antiphospholipid syndrome (APS) is a symptom complex that includes recurrent thrombosis (arterial and/or venous), obstetric pathology (usually fetal loss syndrome) and is associated with the synthesis of antiphospholipids (aPL): lupus anticoagulant (LA), anticardiolipin antibodies (aCL) and antibodies to β2-glycoprotein I (anti-β2-GP-I). The spectrum of neurological disorders associated with aPL production is very wide and includes both ischemic and non-ischemic lesions of the nervous system. The purpose of our study is to identify the relationship between neurological manifestations in pregnant women with APS and the level of aPL, namely aCL, VA, anti-b2-GP I and the presence of other signs of antiphospholipid syndrome. As a result of the study, it was determined that in pregnant patients with a history of APS, antibodies to CL, b2-GP I, and VA were detected with a high frequency. The detection frequency and median values of IgM, IgG to the studied antibodies were significantly higher in pregnant women with APS than in persons from the control group. Moreover, in patients with high titers of aPL, neurological manifestations were observed, such as neurasthenia, migraine, polyneuropathy, chorea and epileptic syndrome, which may indicate primary immune-mediated damage to the nervous system, resulting from the interaction of aPL with phospholipid determinants of the membranes of neurons, glia, and peripheral nerves.

Key words: *antiphospholipid syndrome, pregnant women, antiphospholipid antibodies, lupus anticoagulant, antibodies to b2-glycoprotein I, anticardiolipin antibodies, non-ischemic neurological damage.*

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INTRODUCTION

Antiphospholipid syndrome (antiphospholipid antibody syndrome, lupus antibody syndrome, Hughes syndrome) is a systemic autoimmune disease associated with hypercoagulation and caused by the synthesis of antiphospholipid antibodies (aPL): anticardiolipin antibodies (aCL, lupus anticoagulant (LA), antibodies to b2-glycoprotein I (anti-b2-GP I) [5, 12, 13].

Antiphospholipid antibodies have diagnostic, pathogenetic and predictive significance for both vascular and obstetric APS. Although traditionally, autoantibodies are associated with autoimmune diseases, they are present in minimal quantities in all healthy individuals [1, 6, 7, 9].

Today, the basic diagnostic criteria for APS are:

1. Vascular thrombosis.
2. Pathology of pregnancy.
3. Laboratory criteria:

3.1. The presence of aCL of the IgG and/or IgM isotype in the blood.

3.2. Detection of lupus anticoagulant in blood plasma [2, 3, 4, 11].

A number of neurological disorders in APS not associated with ischemia are a consequence of primary immune-mediated damage to the brain and peripheral nervous system [8, 10]. This mechanism is associated with the occurrence of epileptic seizures, headaches, chorea, a syndrome mimicking multiple sclerosis, neuropathy and some other disorders. Recently, there has been increasing interest in the issue of the relationship between the levels of antiphospholipid antibodies and the presence of neurological disorders in pregnant women [1, 5, 8, 13].

MATERIAL AND METHODS

In this study, 32 pregnant women aged 19 to 38 years (average B 28±1.5) with a history of APS syndrome were examined. The APS Diagnostic Criteria were used to confirm the diagnosis. The control group consisted of 62 healthy pregnant women.

Cerebral pathology was determined clinically, through an objective examination. All patients underwent a standard neurological examination (collection of complaints, medical history, life history, examination of neurostatus).

Immunological studies included determination by enzyme-linked immunosorbent assay (ELISA) of a wide range of aPL of the IgM and IgG classes, antibodies to CL (aCL) of the IgM and IgG classes, β2-GP-I (aβ2-GP-I) of the IgM and IgG classes.

Statistical processing of the obtained data was carried out on a personal computer using a statistical software package (STAT-soft 2022) with the development of the t-Student criterion.

RESULTS AND DISCUSSIONS

Among pregnant women with APS, elevated aPL were found in 92% of women (the absolute number of women was 25), and increased aCL levels were detected in 47% of patients (the absolute number (abs. n.) was 15), while high levels anti-b2-GP I were detected in 31% of women (abs. n. - 10), and VA showed high levels in 12.5% of pregnant women (abs. n. - 4). Antibodies to β2-GP I were detected statistically less frequently than aCL ($p = 0.0165$). The frequency of detection of aPL of the IgG and IgM classes is given in the table. 1

Table 1. Frequency of detection of aPL (IgM, IgG) in blood serum in patients with a history of APS and healthy women when determined by ELISA.

Name of antibodies and class of immunoglobulins	Frequency of detection of aPL in the study groups, abs. n. (%)		p
	patients with APS (n = 32)	healthy women (n = 62)	
anti-b2-GP I IgG	7 (21,8 %)	4 (6,4 %)	0,0104
IgM	3 (9,3 %)	2 (3,2 %)	0,0688
aCL IgG	9 (28,1 %)	3 (4,8 %)	0,3353
IgM	6 (18, 8%)	1 (1,6 %)	0,0571
lupus coagulant	4 (12,5 %)	3 (4,8 %)	0,2007

In the table Table 2 presents the results of determining the level of aPL of both IgM and IgG classes in the blood serum of pregnant women with APS, indicating the median value, as well as the range of values. Median aPL values were statistically significantly higher in pregnant women with APS than in women in the control group ($p < 0.05$).

Table 2. The average level of aPL in the blood serum of pregnant women with APS and healthy women when determined by the ELISA method.

Name of antibodies and class of immunoglobulins	Median aPL level in the study groups, U/ml		p
	patients with APS (n = 32)	healthy women (n = 62)	
anti-b2-GP I IgG	3,1 (0,80-45,7)	1,2 (0,5-7,1)	0,0508
IgM	2,4 (1,1-67,1)	0,8 (0,5-12,3)	0,0337
aCL IgG	2,6 (0,7-33,6)	1,15 (0,5-15,5)	0,0353
IgM	3,7 (1,8-55,6)	1,1 (0,5-7,9)	0,0571
lupus coagulant	3,6 (1,4-21,3)	1,0 (0,8-1,1)	0,0040

Also, during the work, the patients were divided into 2 groups: pregnant women with neurological manifestations of a non-ischemic nature - 26 women and pregnant women without neurological symptoms - 6 women (in percentage terms - 81.3% and 18.7%, respectively).

The range of neurological disorders associated with the synthesis of aPL is very wide and includes, in particular, cerebrovascular accidents and neurological disorders of non-ischemic origin, caused not by vascular, but by primary immune-mediated damage to the nervous system, resulting from the interaction of aPL with phospholipid determinants of the membranes of neurons, glia, and peripheral nerves (phospholipids are universal and important components of nerve tissue membranes) [1, 7, 9].

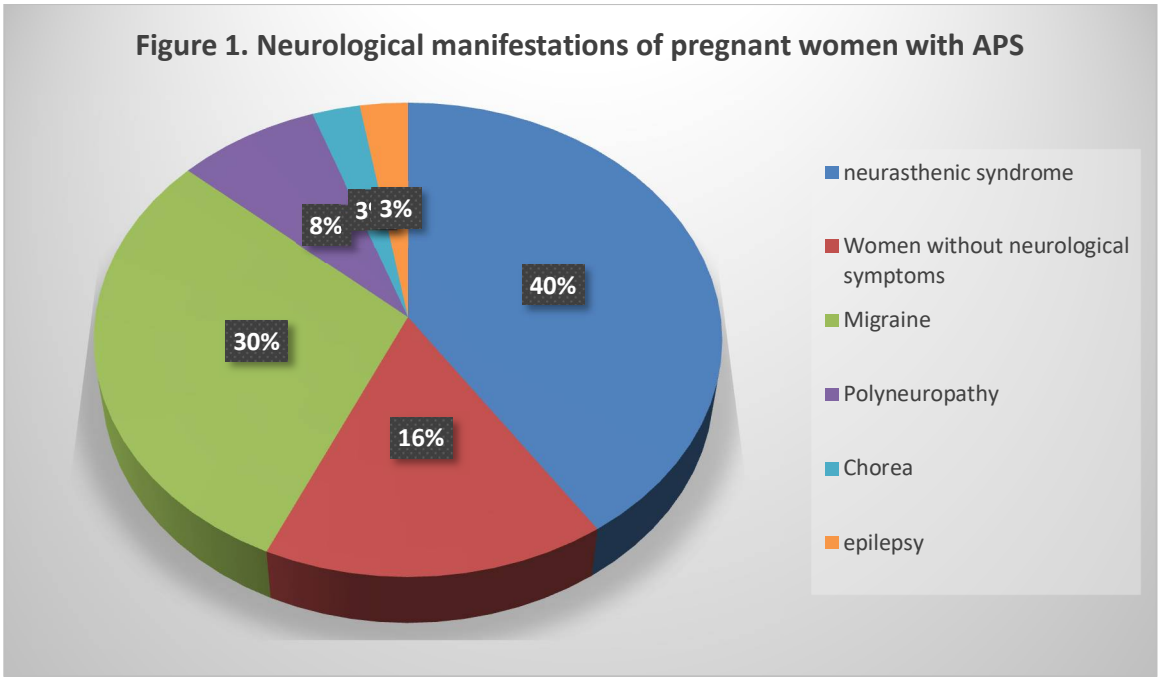
Damage to the brain and peripheral nervous system in patients with primary APS can be caused not only by aPL, but by others - neuron-specific proteins produced in parallel by antibodies, such as myelin basic protein, glial fibrillary acidic protein or neuron-specific enolase, etc. [4, 5, 12].

Among our patients, the following neurological disorders of a non-ischemic nature were identified (Fig. 1): neurasthenic syndrome, which was observed in 15 of our patients (46.9%), and in 6 of them the neurasthenic syndrome was combined with diffuse symptoms of cerebral damage (18.75%). As a result of an objective examination of pregnant women with diffuse symptoms of cerebral damage, a variety of neurological symptoms were revealed, which were manifested by hemiparesis (33.3%), dizziness (66.6%), double vision (16.7%), decreased visual acuity (83. 3%).

Polyneuropathy occurred in 3 patients (9.3%), and this pathology manifested itself as paresthesia, pain in the extremities, decreased superficial sensation, and in the lower extremity's paresthesia was detected in all three patients (100%), while damage to sensory fibers peripheral nerves of the upper extremities were found in only one girl (33.3%). Also, the symmetry of nerve damage was recorded in all of them.

A frequent neurological manifestation in our patients was headache, namely migraine, which was recorded in 11 pregnant women with APS (34.4%). Headaches in our pregnant women most often manifested as migraine without aura (63.6%), less often with aura (36.3%). The severity of headaches in our patients varied. 27% of pregnant women experienced severe migraine attacks. 72.7% of patients had a hereditary predisposition to migraine.

Rarer forms of neurological pathology such as chorea and epileptic syndrome were diagnosed in 1 case each (3.125%). Chorea in our study was manifested by spontaneous movements of the muscles of half the face - hemispasm, which first appeared in our patient during her first pregnancy, which ended in spontaneous miscarriage.



At the same time, the study revealed a connection between high aPL titers and the presence of neurological manifestations in pregnant women with APS. However, the highest levels of AT were in women with polyneuropathy and neurasthenic syndrome, and the median level of anti-b2-GP I exceeded the average values of aCL and VA. At the same time, in patients with chorea and migraine, the average aPL values were minimal compared to those in other neurological pathologies, despite the fact that migraine, along with ischemic brain lesions, are the main neurological manifestations of APS with relatively high aPL values [4, 5, 13].

CONCLUSION

Thus, in pregnant patients with a history of APS, antibodies to CL, b2-GP I, and also VA were detected with a high frequency. The detection frequency and median values of IgM, IgG to the studied antibodies were significantly higher in pregnant women with APS than in persons from the control group. Moreover, in patients with high titers of aPL, neurological manifestations were noted, such as neurasthenia, polyneuropathy, epileptic syndrome, migraine and chorea, which may indicate primary immune-mediated damage to the nervous system, resulting from the interaction of aPL with phospholipid determinants of the membranes of neurons, glia, and peripheral nerves, and not direct vascular damage [1, 7, 9].

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