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ANTIPHOSPHOLIPID PATTERN AS A PART OF THE PATHOGENESIS OF MYOCARDIAL INFARCTION

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A systematic review of the international literature was conducted using the PubMed platform. The purpose of the study was to obtain information about the role of antiphospholipid syndrome in the pathogenesis of myocardial infarction. Acute myocardial infarction is often the first manifestation of antiphospholipid syndrome in young patients. Young patients under 50 years of age without additional risk factors for cardiovascular disease or atherosclerosis of the coronary arteries with recurrent cardiovascular events, including myocardial infarction, should be screened for antiphospholipid syndrome.

Key words: antiphospholipid syndrome, myocardial infarction, acute coronary syndrome, ischemic heart disease, atherosclerosis, thrombosis.

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АНТИФОСФОЛІПІДНИЙ ПАТЕРН ЯК СКЛАДОВА ПАТОГЕНЕЗУ ІНФАРКТУ МІОКАРДА

Проведено системний огляд міжнародної літератури, використовуючи платформу Pubmed. Метою дослідження було отримати інформацію про роль антифосфоліпідного синдрому в патогенезі інфаркту міокарда. У молодих пацієнтів гострий інфаркт міокарду може бути першим проявом атифосфоліпідного синдрому. Молоді пацієнти до 50 років без додаткових факторів ризику серцево-судинних захворювань або атеросклерозу коронарних артерій з рецидивуючими серцево-судинними подіями, зокрема інфарктом міокарду, повинні проходити обстеження на антифосфоліпідний синдром.

Ключові слова: антифосфоліпідний синдром, інфаркт міокарда, гострий коронарний синдром, ішемічна хвороба серця, атеросклероз, тромбоз.

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Antiphospholipid syndrome (APS) is a prevalent acquired thrombophilia that was first described in 1983 [3, 26, 45]. The current understanding (by EULAR-2023) interprets APS as a systemic autoimmune disorder with various vascular manifestations associated with thrombotic and inflammatory mechanisms, triggered by the presence of antiphospholipid antibodies (aPLs), such as lupus anticoagulant (LA), anti-β-2-glycoprotein-1 (anti-β2-GP-1), also known as apolipoprotein H, and/or anti-cardiolipin antibodies (ACLs) [42]. APS, according to ICD-10: R76.2, is defined as chronic recurrent thrombosis in small vessels with secondary ischemia and internal organ failure, triggered by the circulation of auto- and alloimmune immunoglobulins of different classes directed against their own phospholipids (PL).

1–5 % of people in the general population have aPLs, and only a small number of carriers develop APS with autoimmune hemocoagulation disorders. The prevalence of APS is approximately 50 cases per 100 thousand people, and the incidence ranges from 1 to 2 cases per 100 thousand people [14]. The mortality rate of patients with APS is 50–80 % higher than in the general population, and the presence of catastrophic APS is associated with 50 % mortality in a 10-year survival analysis [48].

The purpose of the study was to obtain information about the role of antiphospholipid syndrome in the pathogenesis of myocardial infarction.

The diagnostic criteria for APS were first formulated in 1998 and refined at the ISTH (2006). As part of EULAR-2019, definitions of aPL-titers were approved.

The diagnosis of APS is established in the presence of at least one clinical and one laboratory criterion, and it lacks reliability if the interval between the criteria is less than 12 weeks or exceeds 5 years. In the absence of autoimmune pathology, APS can be primary (7–12 %) and secondary in the presence of autoimmune diseases, infections, oncology, use of medications such as contraceptives, propranolol, chlorothiazide, hydralazine, procainamide, quinidine, amoxicillin, tumor necrosis factor-α (TNF-α) inhibitors, interferon, etc. (88–93 %) [23]; catastrophic (Asherson's syndrome) with rapidly progressive multiorgan thrombosis [6, 25]; in hypoprothrombinemic, microangiopathic and hemolytic uremic syndromes;

seronegative with clinical manifestation in the absence of diagnostic laboratory markers of APS, with recurrent cerebral vascular thrombosis and arterial hypertension (AH) (Sneddon's syndrome) [16].

Table 1

Diagnostic criteria for APS according to Sapporo-2006, Order of the Ministry of Health of Ukraine No. 626, EULAR-2019 Recommendations

1. Clinical criteria for APS:	
Vascular thrombosis	Thrombosis of arteries and/or veins of any localization in the tissue or in individual organs (Doppler or morphologically confirmed)
Pathology of pregnancy	Intrauterine death of the fetus after 10 weeks with normal morphological features, premature birth up to 34 weeks with severe placental insufficiency or preeclampsia, three or more spontaneous abortions up to 10 weeks without hormonal disorders, uterine defects or chromosomal defects
Livedo reticularis (mesh skin pattern) Hemorrhagic syndrome	
2. Laboratory criteria for APS: aPLs (IgG and IgM); LA; thrombocytopenia; false-positive Wasserman reaction.	
Medium and high titers of the aPLs (medium-high aPL titles)	Medium and high titers of IgG/IgM class ACLs in serum/plasma > 40 GPL (MPL), or > 99 per cent (by standardized ELISA)
High risk (high-risk aPL profile)	– positivity for LA in 2 or more cases with an interval of at least 12 weeks (according to the recommendations of the International Society for the Study of Thrombosis and Hemostasis); – double aPLs positivity (in any combination of BA, ACL, and anti-β2-GP-1); – triple aPLs positivity; – isolated persistent positivity of high titers of ACL
Low risk (low-risk aPL profile)	– isolated positivity for ACL or anti-β2-GP-1 in low to medium titers, including transient

Notes: ACL – anti-cardiolipin antibodies, aPLs – antiphospholipid antibodies, anti-β2-GP-1 – antibodies to β2-glycoprotein-I, LA – lupus anticoagulant.

According to the EULAR-2023 criteria [2, 42], the diagnosis of APS is verified in the presence of at least 1 positive test for aPLs within 3 years of the clinical manifestation of APS. Criteria (scored 1–7 points) are grouped into 6 clinical (macrovascular venous thromboembolism and arterial thrombosis, valvular thromboembolism, microvascular manifestations, hematologic changes, obstetric pathology) and 2 laboratory areas (presence of auto-/aloantibodies) [17, 48]. Patients with a score of at least 3 are classified as having APS [50]. In the validation cohort, the new criteria for APS compared to the revised 2006 Sapporo classification criteria are more specific (99 % vs. 86 %) and sensitive (84 % vs. 99 %), respectively [2].

The aPLs, produced by B-cells and directed against certain negatively charged PLs or phospholipid-protein complexes of the cell membrane, affect platelets, immune and endothelial cells, and contribute to the clinical manifestations of APS. For the interaction of aPL with anionic determinants of endothelial cell membranes, the presence of β-2GP-I, which is the main cofactor of aPLs, is required. The main types of aPLs include LA and ACLs, antibodies to proteins that are factors and cofactors of the hemostasis and fibrinolytic system, such as antibodies to anti–β2–GP–1, modified low-density lipoprotein (LDL) [9, 17, 48]. It should be noted that certain aPLs can be informative for the diagnosis of pre-APS and seronegative APS with clinical manifestation in the absence of laboratory markers of pathology [47, 50].

A high level of cross-reactivity between monoclonal aPLs was found. It has been suggested that single transient aPLs can be the cause of many pathological processes and cause various infections, but according to the Sapporo classification, they are not associated with a high risk of thrombotic complications [3].

The paradoxical effect of aPLs has been established: In vitro, aPLs bind to the PL of the prothrombinase complex, preventing thrombin formation and prolonging coagulation, and in vivo, they promote thrombosis [11]. Under the influence of various factors, aPLs can be overproduced and cause the development of APS [4, 23]. Molecular mimicry is one of the mechanisms of APS development. It has been proven that microorganisms contain sequences in their genetic material similar to those in the binding site of β2-GP-I to PL, which leads to cross-reactivity with their own cells [6].

Mostly, APS is associated with persistence of IgG and/or IgM aPLs [14,17]. Asymptomatic carriers of laboratory markers of APS are at high risk of thrombotic events with double/triple aPLs positivity [50]. The association between aPLs and thrombosis is well documented, as it has been established that these autoantibodies are not only markers of APS but are also responsible for inducing the procoagulant phenotype of the disease [9]. Patients with APS have been shown to have a higher percentage of microvascular diseases than the general population [4]. Coronary heart disease (CHD) occurs more often [44].

The classical cardiovascular risk factors cannot fully explain the early occurrence of atherothrombosis in autoimmune diseases, and therefore, the proinflammatory properties of autoantibodies

have been considered as additional risk factors for the development of cardiovascular events. Increasing attention is being paid to APS as an independent factor in the development of coronary heart disease, myocardial infarction (MI) in particular [21, 41, 45].

The purpose of the study: to obtain information about the role of antiphospholipid syndrome in the pathogenesis of MI. To clarify the role of APS and its components in the pathogenesis of MI, we conducted a systematic search of PubMed for 1984–2025 and found 14549 publications on APS, 454 of which analyzed the relationship between MI and APS (85 publications in the last 5 years). It should be noted that the literature review has some limitations: English and Spanish search languages using the PubMed search engine with the keywords "APS and MI".

Most of these studies were related to young patients in whom MI was the first manifestation of APS and was associated with accelerated atherosclerosis in the setting of thrombophilia. According to registries, in APS, MI is observed in approximately 2–5.5 % of affected individuals [5] and is often the first clinical manifestation of the disease [19, 31]. It has been proven that patients with APS have a higher prevalence of CHD compared to the general population, and MI can occur as a result of coronary thrombosis in the absence of severe atherosclerosis, especially among younger people [4, 5, 10, 12, 15, 38, 40].

Experimental studies have revealed the interaction between aPL-mediated mechanisms of atherogenesis, inflammation, and thrombosis in the pathogenesis of CHD and MI, in particular, in APS [28, 44]. Hypercoagulability and thrombosis can be promoted by the ability of APS to activate endothelial cells, platelets, and neutrophils, change the structure of von Willebrand factor, reduce factor XI inactivation and tissue plasminogen activator activity, and increase thrombospondin-1 concentration and factor XII activation [3].

There is a proven link between aPLs and subclinical manifestations of atherosclerosis [18]. Regardless of the presence of classical cardiovascular risk factors, patients with AFB have a higher risk of atherosclerotic plaques in the carotid arteries compared to controls. However, clinical studies have also shown a higher prevalence of traditional cardiovascular risk factors in patients with AF compared to healthy individuals and patients with other chronic cardiovascular diseases such as rheumatoid arthritis and diabetes mellitus [7, 34].

The main target of aPLs is the epitopes expressed on the plasma protein β2-GP-I, which increases its affinity for PL when dimers are formed by reaction with an antibody against β2-GP-I. β2-GP-I is composed of domains; the fifth domain has a positive zone, which is an anchor for anionic phospholipids. β2-GP-I is cleaved by plasmin and activated factor X to form nicked-β2-GP-I (nβ2GPI), which can bind plasminogen and reduce plasmin formation in the presence of fibrin [3]. The positive zone of the fifth domain of β2-GP-1 is an anchor for anionic FLs [13], which are conformationally changed and acquire immunogenicity. aPLs activate general molecules, endothelial cells, monocytes, and platelets [15]; upregulate genes encoding tissue factor and initiate the extrinsic pathway of the coagulation cascade [17]; inhibit fibrinolysis and reduce the activity of activated protein C [16]; lead to the expression of adhesion molecules, downregulation of vasoprotective endothelial nitric oxide synthase and tissue factor inhibitor activity [18, 19]; activate neutrophils by releasing extracellular neutrophil traps (NETs), which are mediators of thrombosis; form immune complexes with phospholipid-binding proteins, activating complement, which increases inflammation and thrombosis [17].

The binding of aPL to β2-GP-I on cell surfaces also upregulates genes encoding tissue factor and cell membrane glycoprotein, initiating the extrinsic pathway of the blood coagulation cascade, and the binding of aPL in endothelial cells leads to a cascade of events with overexpression of adhesion molecules (E-selectin), downregulation of vasoprotective endothelial nitric oxide synthase and inhibition of tissue factor inhibitor activity [39], which induces dysregulation of vascular tone, endothelial dysfunction and enhances platelet adhesion.

APS activates the transcription factor Nuclear factor kappa B (NF-κB), which leads to the expression of E-selectin and provokes the production of cytokines (TNF-a, IL-1b, IL-6) [24, 39], which activate lymphocyte adhesion and lead to the progression of inflammation. Circulating anti-β2-GP-I also increases the expression of tissue factor on the surface of endothelial cells and monocytes, which is a cell receptor and cofactor VII of coagulation factor [6].

aPLs bind to the enzymatic domains of serine proteases (thrombin, activated protein C, plasmin, tissue plasminogen activator, and factor IXa) that form blood clots [11]; interact with the endothelial cell protein annexin A5, which has a high affinity for aPLs, is a natural anticoagulant and marker of apoptosis. The phospholipid membranes of apoptotic cells are bound to annexin A5, which prevents the formation of autoantibodies and a possible excessive procoagulant response. APLs destroy the

"annexin shield" by competing with FLs, such as phosphatidylserine, which contributes to the development of an autoimmune response [6].

aPLs affect the extrinsic and intrinsic pathways of fibrinolysis. Excessive activity of the coagulation system is regulated by complex interactions. Plasminogen is converted to plasmin under the action of tissue and urokinase plasminogen activators, whose activity is inhibited by plasminogen activator inhibitor-1. aPLs lead to endothelial activation and release of tissue plasminogen activator and plasminogen activator inhibitor-1. By interacting with annexin A, APS prevents the binding of tissue plasminogen activator to its endothelial receptor. APS potentially interferes with the normal function of each of the fibrinolytic proteins, contributing to the hypofunction of the fibrinolytic system [6].

APS promote the interaction of von Willebrand factor with platelet glycoprotein Ibα and ApoER2 receptors, increase the production of thromboxane A2, which enhances platelet aggregation; activate the complement system by stimulating C5a synthesis and increasing tissue factor expression, and disrupt thrombolysis through interaction with tissue plasminogen activator and plasmin [3, 27].

The complement system plays an important role in the pathogenetic mechanism of the inflammatory process of cell damage. aPLs form immune complexes with phospholipid-binding proteins, activating the classical complement pathway, increasing inflammation, and complement itself can increase thrombosis by promoting endothelial activation and platelet aggregation [35]. In the acute phase of the disease, the levels of complement C3 and C4 are reduced, but, accordingly, the products of complement activation (C5b-9) are increased. As a result of the action of C3-convertase, the C3 component is broken down into C3a and C3b. On the platelet surface, C3a binds to the receptor and causes platelet activation, adhesion, and aggregation, and C3b enhances phagocytosis and participates in the synthesis of C5 convertase, which cleaves C5 into C5a and C5b. C5a stimulates the expression of tissue factor and plasminogen activator inhibitor-1, and C5b is involved in the synthesis of the C5b-9 complex and its deposition on the cell surface, which leads to cell damage [6].

aPLs activate endothelial cells, platelets, monocytes, and inflammatory molecules [10]; inhibit fibrinolysis and reduce the activity of activated protein C. aPLs activate neutrophils and release their NETs forms, which orresponds to neutrophil cell death and is recognized as a mediator of pathological platelet aggregation and thrombosis [38].

Thus, the pathogenetic mechanisms of aPLs on the hemostatic system can be divided into four groups: activation of endothelial, immune cells, and platelets; inhibition of anticoagulant potential; inhibition of fibrinolysis; activation of the complement system [6].

It has been shown that the presence of elevated aCL titers, in particular anti-β2-GP-I, is independent of conventional cardiovascular risk factors and is recognized as a cause of coronary artery atherosclerosis (CA), an independent risk factor for MI [15] in young premenopausal women and young men.

aCL and anti-β2-GP-I correlate with the severity of ACS. Patients with ACS is comorbid with APS and has a high risk of mortality. However, it should also be recognized that early studies did not prove that aCL is a risk factor for MI, and comorbidity with APS increases mortality in patients with post-infarction cardiosclerosis.

Anti-β2-GP-I has shown prognostic value in arterial thrombosis, including MI, in men due to its proatherogenic effect. Anti-β2-GP-1 stimulates the expression of pro-adhesive, procoagulant, and pro-inflammatory mediators, tissue factor that initiates prothrombin and platelet activation. Several cellular receptors are involved in the realization of the prothrombogenic potential of anti-β2-GP-1: endothelial protein annexin A2, Toll-like receptor TLR4, Apo ER2 receptor, platelet adhesive receptor – glycoprotein Ibα. In most patients with APS, including those with normal titers of aPLs in the blood, autoantibodies to the β2-HP-1/HLA II complex are detected, which are cytotoxic against the cells that formed them [39].

Autoantibodies can also contribute to the development of atherosclerosis [30] by interfering with the protective role of high-density lipoprotein (HDL)and apolipoprotein A-I. Patients with APS often have antibodies against HDL and apolipoprotein A-I, which have been shown to interact with cardiolipin [33].

It has been proven that patients with ACS have a high percentage of aPLs detection, among which anti-β2-GP-I and antibodies to the oxidized LDL/β2-GP-I complex are the most common [8, 9, 3 0]. The interaction between aPL and endothelium causes proinflammatory and procoagulant effects that contribute to the progression of atherosclerosis, and through the cross-reaction of autoantibodies, increases oxidative stress. The complexes formed between anti-β2-GP-I and oxidized LDL may contribute to oxidative and mitochondrial dysfunction, which induces an inflammatory profile and endothelial damage with coronary artery disease and myocardial ischemia, which is consistent with the results of clinical studies that have revealed a relationship between APS and MI with non-obstructive CAD (MINOCA) [38].

According to the CAPS Registry, 28 % of patients with catastrophic APS have a history of MI [10]. The cause of acute MI in the presence of APS in the absence of obstructive lesions of the coronary

artery is considered to be thrombotic microangiopathy [20], which leads to thrombotic cardiomyopathy [13] and left ventricular (LV) remodeling, which correlates with the titer of aPLs [20]. Thrombotic predisposition in APS is explained by activation of endothelial cell adhesion molecules, platelets, proinflammatory cytokines, and endothelial dysfunction due to inhibition of aPLs NO-synthetase.

All the molecular mechanisms involved in the immunopathogenesis of APS remain unknown, but knowledge of additional signaling pathways connecting the innate immune system and the coagulation cascade underlie the pathogenic effects of aPLs on the body, is available. New data indicate a key role of lipid rafts, specific microdomains on the plasma membrane of endothelial cells, monocytes, and platelets, in the signal transduction pathways involved in the pathogenesis of APS. Various signaling pathways triggered by anti-β2-GP-I, involved in the procoagulant effect of aPA, act through lipid rafts. These additional signaling pathways are apparently involved in the induction of the procoagulant phenotype of endothelial cells in patients with ACS comorbid with APS [9].

In the presence of APS, the risk of recurrent MI increases, multiple CAD stenoses with the formation of floating thrombi, restenosis after coronary artery bypass grafting, and subacute stent thrombosis may occur [20, 22, 30, 36].

APS can be considered a risk factor for MI resulting from coronary atherothrombosis in the setting of a persistent thrombophilic state [20], but MI itself can initiate the development of APS, since in the presence of myocardial ischemia, mitochondrial structures of cardiomyocytes are damaged and cardiolipin is released into the circulation, which acts as a trigger for antigen- dependent synthesis of aPLs [43].

It has been found that the mere presence of aPLs in the body is not enough to induce thrombosis. The "two-strike" theory suggests that there must be additional biological triggers (the "first strike" – stress, trauma, infection, surgery, medications, etc.) that lead to activation of the coagulation cascade (the "second strike" – massive release of cytokines, microvasculopathy, and thrombosis).

In experimental conditions, pure aPLs modify the expression of endothelial adhesion molecules and impair vascular function, which is associated with TLR2 and TLR4 signaling, as well as increased production of nitric oxide and tissue factor. Thus, infection or inflammation activates TLR signaling and can increase the expression of aPLs epitopes, which leads to an increased risk of a clinical event [1]. Activation of the TLR2 and TLR4 signaling pathways corresponds to a systemic inflammatory, prooxidative, and prothrombotic state.

It is important to remember that the two-strike hypothesis is a model, not a hard-and-fast rule [3]. The interplay between genetic factors, environmental triggers, and immune responses in ASD is still being investigated, and there is a degree of complexity beyond this simple model [1]. The analysis of 164 men in the Ukrainian population in the postinfarction period revealed an increase in the levels of aPLs and anti-β2-GP-1, which does not contradict this hypothesis. In 56.7 % of patients, low- or cardiac-positive levels of aPLs/anti-β2-GP-1 were detected, including 33.5 % of patients with both low- and medium-positive levels of aPLs and anti-β2-GP-1, in contrast to the control group, in which 29.2 % of patients had low-positive levels of only one of the antibodies [32].

Such an approach to understanding the role of APS components in the pathogenesis of coronary artery disease, in particular MI [28], with an assessment of all levels of aPLs positivity, is consistent with the current understanding of APS diagnosis [17].

How else can the persistence of APS affect the course of the postinfarction period? It has been established that APS are endogenous factors of TLR2/TLR4 toll-like receptor activation, which leads to disruption of the endothelial barrier, increased myofibroblast content in atherosclerotic plaques, and promotes plaque erosion and thrombotic complications [1, 39].

In most patients after myocardial infarction, changes in immunoregulatory processes were detected [43]: increased TLR2/TLR4 expression associated with the carriage of aPLs and anti-β2-GP-1. This is logical, since Toll-like receptors are involved in the realization of the prothrombogenic and endothelial-damaging potential of anti-β2-GP-1 [39]. Increased expression of TLR2/TLR4 in the postinfarction period is associated with myocardial remodeling, which is consistent with experimental data on the involvement of TLR2/TLR4 in the development of interstitial fibrosis and LVH. The formation of an unfavorable immunoinflammatory pattern worsens the course of postinfarction myocardial remodeling, especially in the setting of Q-STEMI and recurrent MI [32].

The pathophysiology of APS involves a complex interaction between the coagulation cascade, the immune system, and endothelial cells. The effect of APS on myocardial health is considered in terms of coronary artery endothelial damage and acceleration of atherosclerosis in the presence of ACLs and anti-β2-GP-1. There is also evidence that APS directly affects the myocardium through mechanisms unrelated to thrombophilia or atherogenesis [13]. In particular, aCL and anti-β2-GP-1 increase

cardiomyocyte apoptosis. In patients with asymptomatic APS, there is a decrease in the myocardial perfusion reserve index and signs of myocardial fibrosis, regardless of the presence of classical cardiovascular risk factors. It is possible that the negative effect of APS on the cardiovascular system can be realized through the activation of toll-like receptors involved in the mechanisms of myocardial remodeling, which accelerates the development of HF. Under these conditions, patients with MI with moderate and high-positive levels of aPLs have a clinically significant deterioration in quality of life compared with patients with negative and low-positive levels of these indicators [32].

APS is characterized by the production of cytotoxic autoantibodies that trigger inflammatory processes. Inflammation, immunity, and thrombosis are separate pathogenic pathways of APS and MI development with numerous points of intersection [35, 49]. The immune response, as a nonspecific first line of defense, relies on the complement system and immune cells, which, upon activation, release cytokines such as IFN-I, TNF-α, and IL-1, which provokes and trigger an inflammatory response. At the same time, insufficient degradation of DNA-containing neurotransmitters and impaired clearance of apoptotic cells lead to the accumulation of nuclear residues that can be a source of autoantigens. Immune complexes containing autoantibodies attached to cellular residues can activate plasmacytoid cells and produce large amounts of IFN-I, which is a factor in maintaining the inflammatory process [43, 44].

Aberrant activation of neutrophils causes the release of reactive oxygen species and various proteases, which also contributes to cell damage. In addition, activated neutrophils can secrete cytokines and chemokines, further exacerbating autoimmune aggression [39]. Autoantibodies can provoke regulatory dysfunction of T cells, which leads to increased levels of proinflammatory interleukins such as IL-6. Tissue infiltration by T lymphocytes and deposition of immune complexes initiate a cascade of inflammatory reactions, activating the complement system, promoting cytokine production, which leads to destruction of the extracellular matrix by matrix metalloproteinases. And only over time does tissue repair occur through fibrosis, also under the influence of cytokines such as transforming growth factor β [39].

Autoantibodies provoke hypercoagulability and establish a bidirectional relationship between thrombosis and inflammation. On the one hand, immunothrombosis with over-expression of the inflammatory response leads to thrombotic activity. Complement activates platelets, and they provide a surface for complement activation. In addition, platelet-bound complement enhances the pro-inflammatory effect of immune cells. On the other hand, there is thrombin inflammation with platelet activation and the coagulation cascade, which leads to the involvement of additional immune cells in the pathological process. The interaction between inflammation and thrombosis results in a vicious cycle of coagulation and activation of immune inflammatory cells [43, 44].

A thorough understanding of all these mechanisms helps to optimize the treatment of APS [39]. Anticoagulant therapy (vitamin K antagonists (VKAs) and direct oral anticoagulants – antifactor Xa/antifactor IIa) is the basic therapy due to the increased incidence of thrombotic complications, in particular atherothrombosis in myocardial infarction, and their recurrence. In patients with APS, current guidelines recommend AVC, based on the higher incidence of arterial thrombosis than venous thrombosis with direct oral anticoagulants compared to LMWH. However, it should be noted that in addition to anticoagulant effects, factor Xa inhibitors, such as apixaban and rivaroxaban, can inhibit inflammation and reduce the expression of proinflammatory mediators [20]. It is also known that arterial thrombosis can be caused by damage to the double-stranded DNA of endothelial cells, so a factor IIa inhibitor (dabigatran), which can repair DNA breaks, may be more effective than factor Xa inhibitors. Low-molecular-weight heparins and antiplatelet drugs are relevant for existing APS.

In addition to anticoagulants, treatment with biologics has been proposed.

Since B-lymphocytes produce antibodies to aPLs, monoclonal antibodies specifically targeting B cells may be a viable treatment option. Rituximab and obinutuzumab, monoclonal antibodies to the B-cell surface antigen CD20, are used to reduce aPLs titers and, in the second order, modulate T helper activation. The binding of monoclonal antibodies to the transmembrane antigen of B- B-lymphocytes CD20 activates immune responses and causes lysis of B-lymphocytes; reduces the expression of CD40 and CD80 antigens on the surface of B-lymphocytes, inhibits T-lymphocyte activation, and restores autotolerance.

Daratumumab, a human IgG1-kappa monoclonal antibody targeting CD38, is recommended for use in the absence of response to standard immunosuppression and anticoagulant therapy. Belimumab, an IgG1λ monoclonal antibody specific for soluble circulating B-cell stimulatory protein (BLyS), which is a factor in B-cell survival, has proven to be useful in high thrombotic risk and microthrombotic complications. The monoclonal antibody blocks the binding of BLyS to B-cell receptors, reduces the differentiation of B cells into plasma cells that produce immunoglobulins, and inhibits B-cell survival.

Eculizumab affects complement: it can inhibit the formation of the membrane-attacking complex and prevent the cleavage of complement C5, activation of the cascade system of proteolytic enzymes, and platelet aggregation. Anti-TNF-α therapy with adalimumab or certolizumab has an antithrombotic effect by inhibiting TNF-α, induced by anti-β2-GP-I, and reducing endothelial dysfunction.

The use of antioxidants with or without concomitant glucocorticosteroid therapy is a possible therapeutic option that leads to a decrease in cytokines and autoantibodies due to the existing clustering between inflammation, oxidative stress, and immune dysregulation in APS [49].

Conclusions

Thus, this literature review demonstrated the demographic data and pathogenetic features of MI in comorbid patients with APS.

Evidence is presented that the pathogenetic basis of MI, especially in young people comorbid with APS, may be the interaction of aPLs with β2-GP-I, which triggers a cascade of cellular reactions and causes inflammation and thrombosis. The target of aPLs is the epitopes expressed on the plasma protein β2-GP-I, which is related to PL when it forms dimers through a reaction with an antibody against β2-GP-I.

Regardless of gender, patients under 50 years of age, even without additional risk factors or atherosclerotic lesions of the coronary artery, who have recurrent cardiovascular events, including MI, should be screened for APS.

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TRANSFORMATION OF PRIMARY DISABILITY INDICATORS DUE TO EPILEPSY UNDER MARTIAL LAW

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The problem of disability remains painful for all countries of the world, both from a medical and socio-economic point of view. Diseases of the nervous system, especially epilepsy in people of working age, are a significant problem in Ukraine. The ongoing war is expected to exacerbate this problem. The study aimed to analyze trends in disability due to epilepsy in wartime settings to identify causal patterns of disability. In this article, disability due to epilepsy is considered one of the essential medical and social characteristics of public health in wartime. The relevance of this problem in our country is due to its significant scale and negative dynamics, especially at the expense of working-age people.

Key words: epilepsy, primary disability, working and adult population, military status.

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ТРАНСФОРМАЦІЯ ПОКАЗНИКІВ ПЕРВИННОЇ ІНВАЛІДНОСТІ ВНАСЛІДОК ЕПІЛЕПСІЇ В УМОВАХ ВІЙСЬКОВОГО СТАНУ

Проблема інвалідності залишається болючою темою для всіх країн світу як з медичної, так і з соціально-економічної точок зору. Захворювання нервової системи, особливо епілепсія у людей працездатного віку, є значною проблемою в Україні. Очікується, що війна, яка триває, загострить цю проблему. Метою дослідження було проаналізувати тенденції інвалідності внаслідок епілепсії в умовах воєнного часу, для виявлення причинно-наслідкових зв'язків інвалідності. У цій статті інвалідність внаслідок епілепсії розглядається як одна з найважливіших медико-соціальних характеристик громадського здоров'я у воєнний час. Актуальність цієї проблеми в нашій країні зумовлена її значними масштабами та негативною динамікою, особливо за рахунок осіб працездатного віку.

Ключові слова: епілепсія, первина інвалідність, працездатне та доросле населення, військовий стан.

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Neurological disorders are the leading cause of disability-adjusted life years (DALYs) lost and the second leading cause of death worldwide, with 9 million people dying from neurological disorders each year [8–11]. In 2016, the top five neurological causes of DALYs were stroke (42.2 %), migraine (16.3 %), dementia (10.4 %), meningitis (7.9 %), and epilepsy (4.9 %) [19–21]. Neurological disorders are now the second leading cause of death and the leading cause of disability worldwide. A new, groundbreaking study, Global Burden of Disease (GBD), shows that the number of people living with brain diseases will double by 2050 [12, 21–23, 26–29].

The Global Burden of Disease (GBD) study identified the 10 most disabling neurological diseases worldwide, including data on the 36 most common neurological disorders and conditions, and provides estimates of prevalence, years lived with disability (YLD), years of life lost (YLL), and disability-adjusted life years (DALY) for each condition. Currently, about 90 % of the total neurological DALYs are accounted for by 10 primary conditions: stroke, neonatal encephalopathy, migraine, dementia, meningitis, epilepsy, neurological complications associated with preterm birth, nervous system cancer, autism spectrum disorders, and Parkinson's disease [5, 7, 19–20, 28].