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CURRENT PERSPECTIVES REGARDING THE IMMUNOLOGICAL INTERACTIONS BETWEEN APS AND SARS-COV-2

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ABSTRACT

Autoimmune diseases are commonly known for their difficult diagnosis. Currently it is known that these pathologies arise as a result of a set of factors. Among them are the genetic and environmental factors, in addition to the failure of one's body immune system. The failure in the immune system is mainly associated with molecular mimicry which causes the defense cells to attack the body as an attempt to perform a biological protection. Furthermore, it is known that among the environmental factors, the viral infections stand out as potential triggers to the autoimmunity process, since viruses have several mechanisms to block the performance of regulatory T cells and induce the production of inflammatory cytokines. COVID-19 is an infectious viral disease caused by the SARS-CoV-2 virus. Patients infected with the virus are more susceptible to arterial and venous obstruction based on thrombotic fibrin. Thus, individuals infected with SARS-CoV-2 have an increased likelihood to develop the Antiphospholipid Antibody Syndrome (APS). APS is an autoimmune disease associated with the development of hypercoagulability, high serum levels of antiphospholipid antibody and is responsible for the occurrence of important thrombotic processes in individuals affected by the pathology. Furthermore, it is known that individuals with APS have a higher risk of suffering from acute myocardial infarction as a consequence of disease complications. The aim of this study is to evaluate the clinical and immunological characteristics of patients with antiphospholipid syndrome (APS) and to investigate its possible association with the SARS-CoV-2 virus.

Key words: Autoimmune diseases, Immunology, Antiphospholipid syndrome, Virus.

1.0 INTRODUCTION

1.1 Autoimmune diseases (Introduction)

Autoimmune diseases are found in about 5% of the world population, they are usually identified by the elimination of other pathologies through highly sensitive biomarkers, since they can be easily mistaken for viral, bacterial, parasitic infections or other infectious agents, which means that they are almost never the first diagnostic hypotheses. Jara (2020) They are more frequent in females, represented by approximately 70% of those affected due to the estrogen hormone. In addition, it is known that it appears more often between 16 and 55 years old, and also their clinical characteristics tend to vary a lot depending on the ethnic group of the patient. Merrheim *et al*., (2020).

The development of autoimmune diseases is characterized by a set of genetic and environmental factors, such as infections, and the failure of the immune system. The latter's primary function is to recognize in the body what is a Self cell, represented by innate cells of the organism itself and recognizing what is a non-Self cell, which can be described as cells which do not belong to the organism. Furthermore, the immune system can be divided, triggering two types of immune responses, a central and a peripheral one.

Central tolerance happens in the thymus and bone marrow Merrheim *et al*., (2020) and its failure occurs due to molecular mimicry. When peptides that are not common to the organism share homology and cause the production of self-antigens, which will lead to the activation of self-reactive agents to fight them Jara (2020). Peripheral tolerance, on the other hand, happens in the lymph nodes, spleen and mucous membranes and is triggered by external factors such as viral infections, nutrition, sun exposure, melatonin levels, lifestyle, drugs, other chemicals and pollution. Failure of central and / or peripheral tolerance can lead to autoimmune disease.

1.2 Self-Tolerance associated with molecular mimicry unleashed by external agents

These immune responses responsible for self-tolerance are counterbalanced by regulatory T cells (Tregs), which are able to suppress the production of inflammatory cytokines, the proliferation of cytotoxic T cells, and antigen presenting cells (APCs). Chiu et al., (2016) The increased production of IL-6 can induce the dysfunction of regulatory T cells by converting them into 'effector' Th17 cells as well as inducing a pro-inflammatory Th1 response. It is known that the production of IL-6 can be induced by infections triggered by respiratory viruses acting as a strong environmental factor for several types of autoimmune diseases since respiratory infections triggered by viruses will trigger Tregs dysfunction. Chiu et al., (2016)

1.3 Molecular mimicry associated with self-tolerance induced by antiviral vaccines

The application of vaccines with live-attenuated viruses (LAV) directly relates to autoimmune responses in patients that the organism triggers the process of

molecular mimicry Elwood (2018). If the organism keeps producing a high volume of mediators against the attenuated viruses, this shifts the targeting of a large part of the cells of the immune system to develop pathological functions, which results in tissue damage Crow (2019). As a consequence of vaccination, these individuals end up developing diseases such as: rheumatoid arthritis, systemic lupus erythematosus, thyroid diseases, among other responses that are considered to be autoimmune. Elwood (2018)

1.4 Viral infections as an important trigger to the development of autoimmunity

Viruses pose themselves as one of the main environmental factors that trigger responses of the immune system to the organism itself. Thus, the association between the development of autoimmune diseases triggered by viral infections can be tightly related. Allen *et al*., (2018)

The epstein barr virus (EBV) is related to the development of Systemic **lupus erythematosus** Kaul *et al*., (2016). It has been also noted that patients who were infected with EBV developed rheumatoid arthritis; in this group of infected people, when compared to the control group, a viral load of infection 10 times higher could be seen when compared to individuals who had rheumatoid arthritis but were not infected with EBV. Balandraud (2018)

Patients with autoimmune diseases are more likely to develop infections, which can be caused by bacteria or virus. This fact is due to the use of immunosuppressant medications such as corticosteroids to prevent one's immune response from being activated against cells of the body itself. Askanase (2020)

Autoimmune individuals who take immunosuppressants are more vulnerable to SARS-CoV-2 infections. However, the interruption of the use of these drugs is still no appropriate to prevent an aggravation of the disease, and can also lead to a consequent increase in the risk of other infections. However, the use of medications must follow a multidisciplinary treatment, be strictly monitored and managed according to the patient's clinical and serological characteristics. Diamanti (2020)

Patients who are infected by viruses (SARS-CoV-2) particularly shows a delay in the immune response by cytokines, such as type I interferon, which slows down the immunological action of granulocytes, thus causing an exacerbation of the immune system when tissue damage is already done. In individuals with autoimmune diseases taking immunosuppressants, the involvement of parenchymal tissue is even greater, since there is already an innate tendency to inhibit defense cells, intensifying viral replication. Nikpour (2020)

The largest international prospective cohort study conducted with more than 8676 newborns by Lonnrot *et al*. (2017) reported the development of pancreatic islet autoimmunity after recurrent respiratory infections. Not only that but also patients with fever showed a higher risk associated with islet autoimmunity compared to non-febrile patients, so fever can be a factor that increases the risk of pancreatic islet autoimmunity. Furthermore, a study by Favalli *et al.,* (2020) showed that the

group of coronaviruses and parainfluenza viruses are associated with the development of rheumatoid arthritis. This confirms the correlation between respiratory viruses as potential triggers for autoimmune diseases.

Antiphospholipid Antibody Syndrome (APS) is the most common autoimmune pathology responsible for causing thrombophilia, with a prevalence of around 40 to 50 cases in 100,000 worldwide, and its incidence is 5 patients in 100,000. Its main characteristics are as follows: gestational morbidity (constant abortions), hypercoagulability, in addition to presenting high serum levels of antiphospholipid antibody (AFA). This syndrome can be classified into two groups: primary and secondary. Primary APS is characterized only by the syndrome, with no underlying condition, with higher levels of serum type 1 interferon, while the secondary happens when there is the syndrome associated with another autoimmune disease, systemic lupus erythematosus being the main associated disease Nakamura *et al.,* (2018). However, it is often not possible to distinguish in secondary APS whether the first disease to show up was APS or another autoimmune disease. Nakamura *et al.,* (2018)

The syndrome can progress to a more advanced stage, which is called acute or catastrophic APS, in which there is a predilection for platelets, endothelial cells and cells of the placenta (trophoblast), which causes placental insufficiency. Peterson *et al.,* (2016) According to The Brazilian Journal of Rheumatology, the population of primary APS has a higher frequency of arterial thrombotic phenomena, more specifically Sneddon's syndrome, an unknown systemic vascular disease in which there is involvement of medium and small caliber arteries and extremity ischemia, in relation to patients with secondary APS. It also reinforces the role of autoantibodies in identifying subgroups of APS associated with SLE. Levy (2017)

APS has three main antibodies: lupus anticoagulant (LA), which is the most thrombotic, anticardiolipin (aCL), which shows greater sensitivity in laboratory tests, and anti-b2-glycoprotein (anti b2-GPI). These are important risk predictors and their high levels provide substantial risk. When there is a triple positive there is a substantially high risk of thrombosis. Litvinova *et al.,* (2018)

The coagulation process is mediated by prothrombin or factor II, a protein produced by the liver responsible for the conversion of fibrinogen into fibrin, important in secondary homeostasis which in association with platelets promotes blood clotting. When the tissue is restored, the clot is degraded breaking up into fragments of fibrin called the D-Dimer.

However, examination of the D-Dimer is necessary to identify its presence and consequently the presence of thrombi, along with the clotting time, which aims to determine the blood clotting tendency, a mandatory test in patients with APS. This is proven by Bao *et al*. (2017) where pregnant women with recurrent fetal loss show very high serum D-Dimer numbers when compared to the standard level in healthy women established by the study.

The occurrence of acute myocardial infarction in patients with APS is very outstanding, since acute coronary

disease is one of the first manifestations of the disease, occurring in 80% of patients, mainly women over 30 years of age. This shows that the aCL antibody is a factor that predisposes the occurrence of AMI (acute myocardial infarction) in young adult patients, which proves that APS with high levels of aCL causes cardiomyopathies. Kolitz *et al.,* (2019)

Anticardiolipin antibodies, lupus anticoagulant and anti-b2-glycoprotein are the main antiphospholipid antibodies found in the processes of formation of venous and arterial thrombi in tests to confirm APS. These are important risk predictors and their high levels provide substantial risk.

There is a phospholipid present in the cell membrane called Phosphatidylserine (FS), it is present in the intracellular medium, with the exception of trophoblastic cells, in these cells the FS is facing the extracellular medium. When the FS is in an extracellular environment, it binds to the beta2-glycoprotein I, activating the complement system, along with the antibody, inducing the release of tissue factor into platelets and endothelial cell activities, and this triggers the coagulation cascade, initiating a thrombotic state.

2.0 General Objectives

This study aims to trace clinical and immunological characteristics of those presenting Antiphospholipid Antibody Syndrome (APS) and to evaluate the syndrome's relation with the virus SARS-CoV-2.

2.1 Specific objectives

- Provide an update about the interactions between viral infections and autoimmune diseases.
- Evaluate clinical abnormalities in patients with Antiphospholipid Antibody Syndrome infected with SARS-CoV-2.
- Analyse the development of autoimmunity in relation to respiratory viruses.
- Identify different immune responses unleashed in different age groups.
- Analyse the probable prevalence of gender related to autoimmune diseases.
- Associate the COVID-19 infection to the development of Antiphospholipid Antibody Syndrome.

3.0 METHODOLOGY

The relevance of this study was established by assessing the impact index of the journals used addressing the association between respiratory infections associated with the development of autoimmunity in an analysis of the last 5 years through the Scielo and Medline databases via Pubmed. The selected articles presented information related to APS, autoimmune diseases triggered by respiratory viruses and the group of Coronaviruses and their possible viral association with the development of autoimmunity. The impact factor of the journals, determined from Qualis - degree of importance of a magazine in Brazil in which each article was published, acted as a preponderant factor for the definition of the degree of relevance of the present studies used.

4.0 Results

Research was made in the Medline database (Pubmed). The articles were selected after reading the titles and abstracts. The inclusion criteria consisted of articles published in the last 5 years, in English or Portuguese and carried out in humans. As an exclusion criterion, only studies that did not address viral infections associated with the development of autoimmunity, studies that did not address immunological aspects of APS, studies that refer to autoimmune diseases related to other topics that did not involve the immunological profile and studies that did not addressed the SARS-CoV-2 immune pathway were dismissed. Through the different search criteria, the following results were found. Regarding the Boolean operators used, " autoimmune diseases " determined the frequency of 38.46%, " Immunology " and " Antiphospholipid syndrome " accounted for 23.07%, " virus " accounted for 16.66% followed by 7.69% of the words " antiphospholipid antibody ", " immunological tolerance ", " Antibody-antiphospholipid ", " COVID19 ", " Autoimmune ", " Respiratory ", " phosphatidylserine ", " heart ", " dimer ". As for the journals used, " Autoimmunity Reviews " represented 16.66%, " Current opinion in rheumatology " and " International Journal of Molecular Sciences " represented 11.11% and 5.55% represented the other journals: " Lupus Science & Medicine ", " Vasa ", " Diabetologia ", " The Journal of Immunology ", " Annals of the Rheumatic Diseases ", " Thrombosis Research ", " medRxiv ", " Vaccine ", " Reviews in medical virology ", " Annual Review of Pathology ", " Joint Bone Spine ", " Advances in clinical chemistry ", " Arthritis care & research " and " Frontiers in immunology ".

5.0 DISCUSSION

One of the causes to trigger an immune response against the organism itself is the environmental factor; mainly associated with viral infections. Allen *et al.,* (2018) Viral infections can precede the symptoms and the real characteristics of an autoimmune disease and modify the innate and adaptive immune response, through several mechanisms, including: molecular mimicry, epitope dispersion and B cell intensification. Jara *et al.,* (2018)

Resulting in an overproduction of antibodies like those found in autoimmune diseases. Some viruses have been found to trigger the central nervous system, consequently to an associated autoimmune disorder. Patients with multiple sclerosis or other types of demyelinating disorders in most cases test positive for the epstein barr virus, which is directly associated with the development of autoimmunity. Jara *et al.,* (2018)

It is estimated that 1 to 5% of the world's population has lupus anticoagulant (LA) with a higher prevalence in the elderly. Linnemann (2018) However, not all patients will have an advanced stage of the disease, considering these people adopt a healthy lifestyle like not using tobacco, having a good nutrition, doing physical activities, suspending the use of hormonal contraceptives and controlling pre-existing diseases. Peterson *et al.,* (2016) The concomitant positivity antiphospholipid antibodies (APL)

observed in infectious events is low and can be transient. However, the risk for vascular events or adverse pregnancy outcomes increases when there is positivity for the three components of APLs: LA, ACL and anti-b2GPI. Linnemann (2018)

The syndrome that generates thrombotic events has the pathophysiology of disruption of endothelial integrity caused by external factors and oxidative stress. The main APL is b2GPI which acts as the main natural anticoagulant, action on the innate immune response. The increase in oxidative stress alters the conformation of b2GPI. Higher numbers of these antibodies increase the immunogenicity of T cells, which results in the generation of pathogenic antibodies. After that, thrombus formation occurs in the accumulative action of immune complexes b2GPI-anti-b2GPI in endothelial cells, platelets, monocytes and neutrophils, exposing procoagulant phosphatidylserine. Obstetric APS causes thrombosis and intraplacental infarction, which are the results of inflammatory processes, alteration in the function of annexin A5, activation of the complement system, inhibition of syncytium-trophoblast differentiation, interruption of normal function of trophoblast and endothelial and defects in placental apoptosis. Linnemann (2018)

The most evident clinical presentation of the syndrome is DVT (deep vein thrombosis), but it may also develop mild or moderate thrombocytopenia, pulmonary thromboembolism, AMI (acute myocardial infarction), neurological disorders such as stroke and neuro-psychiatric manifestations, as well as renal manifestation and livedo reticularis. Peterson *et al.,* (2016) In addition, the manifestations of obstetric SAF are: spontaneous abortions, late pregnancy complications such as pre-eclampsia, HELLP syndrome (hemolysis, elevated liver enzymes and low platelet count), premature delivery and intrauterine growth restrictions due to uterine failure. Linnemann (2018)

The diagnosis of APS is performed through laboratory tests that analyze LA, ACL, anti-beta2GPI, IgG or IgM through the ELISA method. Serological tests should be done every twelve weeks, as there may be false positives or negatives. As such, clinical events should be minimally studied. Nakamura *et al.,* (2018) In thrombotic episodes, the use of heparin along with coumarins is indicated, monitoring the INR, an exam used to check the effect of warfarin in the blood, until it arrives at the normal rate, followed by the removal of heparin. In patients with positive SLE and APS, treatment begins before presenting the symptoms of thromboembolism, since early treatment decreases the chances of causing the first event, thus the use of low doses of aspirin (100mg / day) and hydroxychloroquine since it showed to be beneficial due to its heart protection. Litvinova *et al.,* (2018).

Similarly, it is known that during autoimmune syndromes there is a hypothesis that triggers, such as viral infections guide the activation of an exacerbated innate and acquired immune response, with a high rate of production of cytokines mainly TNF-a, IL-1β, IL-17, IL-18 and IL-6 in genetically predisposed patients. Therefore the

pathological and immunological mechanisms associated with SARS-CoV-2 suggest that this virus may act as a trigger for the development of an autoimmune and autoinflammatory dysregulation in patients who have a genetic predisposition. Allen *et al.,* (2018)

COVID-19 is an infectious viral disease, caused by the SARS-CoV-2 virus which reaches the respiratory tract and predisposes patients with some pre-existing prothrombotic disease. However, patients infected with the virus are more susceptible to arterial and venous obstruction based on thrombotic fibrin. Galeano-valle *et al.,* (2020)

In a recent study by Qin; C et al., 2020, in which 452 patients had SARS-CoV-2 infection, the majority of them had elevated inflammatory cytokines such as tumor necrosis factor (TNF) - a, interleukin (IL) -1 and IL-6. In addition, high serum levels of these cytokines were found in infected patients with severe clinical status, compared to non-severe patients.

In addition, a decrease in TCD4+ and TCD8+ cells was observed in individuals who were clinically more severe, in addition to a decrease in Treg cells, which possibly can be explained due to the high expression of pro-inflammatory cytokines in patients with COVID-19. Allen *et al.,* (2018) A process similar to what occurs in the development of autoimmune diseases due to the deregulation of Tregs.

The antiphospholipid antibody targets SELF phospholipid proteins, a factor that corroborates an eventually fatal thrombophilia due to the appearance of pathogenic autoantibodies. As a result of the research carried out by ZUO, Y et al., (2020) it was observed that COVID-19 becomes positive for aPL, which are potentially pathogenic. Zuo *et al.,* (2020)

It is seen that some HLA proteins (Human Leukocyte Antigen) predispose patients to certain types of viral infections, as in the case of influenza A (H1N1). However, according to a research by Diamanti *et al.,* (2020) on other coronaviruses, they do not show a significant relationship between the HLA protein and coronavirus infections; these conclusions can be extended to SARS-Cov-2. Diamanti *et al*., (2020)

It has been seen that in patients infected with SARS-CoV-2 the proteome of the virus shares some amino acid sequences with proteins located in the medulla of the brainstem, which is the respiratory center of the human body. This highlights the relationship seen between the attack of inflammatory cells, and respiratory depression, since when attacking the virus, cytokines can also signal an attack on the proteins that regulate breathing. Rodríguez *et al.,* (2020)

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