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CIRCULATING LEVEL OF INTERLEUKIN 6 IN PATIENTS WITH PRIMARY ANTIPHOSPHOLIPID SYNDROME

By

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ABSTRACT

Background: The antiphospholipid syndrome (APS) is an autoimmune systemic disorder that carries many mortality and morbidity. Many cytokines come up in APS; IL6 is one of this cytokines.

Objective: Assessing Circulating Level of Interleukin 6 (IL 6) and its relations to thrombotic risk in patients with primary APS.

Patients and Methods: This study was carried out on sixty patients suffering antiphospholipid syndrome, and thirty healthy volunteers as a control. They were selected from inpatient and outpatient clinic of Internal Medicine and Unit of Immunology Departments from Al-Azhar University Hospitals (Al-Hussein, New Damietta and Al-Azhar University Hospitals), during the period from November 2017 to December 2019. They were divided into three equal groups: Group A; suffering from primary APS, Group B; suffering from secondary APS, Group C; healthy normal volunteers as a control group. All patients and controls were subjected to complete history, clinical assessment and laboratory investigations. Serum level of interleukin-6 was assessed.

Results: There was a statistical significant increase in IL6 among patients with 1ry APS as well as patients with 2ry APS. The commonest presentation among our studied patients with 1ry APS was venous thrombosis (17%) arterial thrombosis (9%) and unexplained abortion (10%). The significant signs that were detected on general examination of those patients were livedo reticularis (10%), Raynoud phenomen (15%) and purpuric eruption (13%). As regard 2ry APS, the commonest presentation among studied patients was venous thrombosis (23%) arterial thrombosis (24%) and unexplained abortion (12%). The significant signs detected on general examination of those patients were livedo reticularis (6%), Raynoud phenomen (10%), and purpuric eruption (13%). As regard the mean IL-6, there was a high significant difference between 1ry APS, 2ry APS and control groups ($P<0.001$). This study showed a positive correlation of IL-6 with arterial thrombosis among patients with 1ry APS. No correlation was detected between IL-6 and arterial thrombosis among patients with 2y APS. Regarding the correlation between venous thrombosis and IL-6 in patients with 1ry APS and 2ry APS, there were no statistically significant positive correlations as regard IL6.

Conclusion: IL-6 was found in patients to be elevated with primary APS. Serum IL-6 was showed to be positively correlated with arterial thrombosis.

Keywords: Interleukin 6, Antiphospholipid Syndrome, cytokines.

INTRODUCTION

The antiphospholipid syndrome (APS) is an autoimmune systemic disorder characterized by thrombosis and obstetric morbidity associated with persistent antiphospholipid antibodies (aPL) *(Cervera et al., 2015)*. Clinically, it causes venous and/or arterial thrombosis affecting blood vessels throughout the body, resulting in significant morbidity and occasionally mortality. The obstetric manifestations include three or more consecutive unexplained miscarriages, one or more unexplained death of a normal fetus at or beyond the 10^{th} week of gestation, evidence of placental insufficiency or one or more premature birth of a normal neonate before the 34^{th} week of gestation because of eclampsia or preeclampsia, or evidence of placental insufficiency (Sada et al., 2015).

APS has varied clinical features and a range of autoantibodies. Virtually any system can be affected *(Abreu et al., 2015)*. Additional clinical manifestations which are not included in the classification criteria (referred to as non-criteria manifestations) may be observed such as livedoreticularis; neurological manifestations, nephropathy, thrombocytopenia and heart valve disease even though they are not included in the classification criteria. The kidney is a major target organ in APS. However, it has not received much attention because of the common association between APS and systemic lupus erythematosus (SLE), which has historically, focused studies on immune-complex-mediated glomerulonephritis rather than renal vascular lesions. There are many clinical presentations, due to both large vessels (arterial and venous) and microvasculature involvement *(Sciascia et al., 2017)*.

Close interaction between immune and haemostatic systems is an attempt to restore normal tissue function following injury. Local activation of the haemostatic system is an essential part of the host defence in both infectious and non-infectious inflammatory states. However, an exaggerated and insufficiently controlled haemostatic activity induced by inflammation may appreciably contribute to disease severity *(Margetic, 2012)*.

Patients with definite APS had significantly higher TNF-a levels than normal controls, in line with previous results.37 In addition, elevated TNF-a levels correlated positively with IL-6 in patients with previous venous thrombosis. It has been suggested that aPL and TNF-a might co-operate in inducing endothelial perturbation *(Rheumato et al., 2016)*.

In addition, *Ogata et al. (2011)* showed that two major function of IL-6 are reported; Firstly, IL-6 acts as a growth factor of some malignant and non-malignant cells such as malignant plasma cells in multiple myeloma. Secondly, IL-6 mediates inflammatory and immune responses in rheumatoid arthritis, psoriasis, cardiac myxoma and other inflammatory conditions.

In addition, *Nishimoto et al. (2012)* showed that IL-6 is a pleiotropic cytokine with a wide range of biological activities such as support of hematopoiesis, regulation of acute phase reactions, and generation of immune responses.

Interleukin 6 (IL-6), promptly and transiently produced in response to infections and tissue injuries, contributes

to host defense through the stimulation of acute phase responses, hematopoiesis, and immune reactions. Although its expression is strictly controlled by transcriptional and posttranscriptional mechanisms, dysregulated continual synthesis of IL-6 plays a pathological effect on chronic inflammation and autoimmunity *(Tanaka et al., 2014)*. Also, *Rauch et al. (2018)* stated that patients with autoimmune aPL or primary APS show a predominance of Th2-type response evidenced by a significant increase in serum levels of IL-6.

The aim of this work was to evaluate circulating Level of Interleukin 6 (IL 6) and its relations to thrombotic risk in patients with primary APS.

PATIENTS AND METHODS

This study was carried out on sixty patients suffering antiphospholipid syndrome and thirty healthy volunteers as a control in the period from November 2017 to December 2019.The patiants and control were divided into following groups: Group A: Include thirty patients suffering from primary APS. They were diagnosed as primary APS based on recent the revised classification criteria for definite primary APS which include the presence of at least one clinical and one laboratory criterion ensures the diagnosis even in the presence of other causes of thrombophilia *(Brandt et al., 1995)*.Group B: Include thirty patients suffering from secondary APS suffering from a connective tissue disease (including SLE).Group C: Include thirty healthy normal volunteers matched for age and sex as a control group.

All procedures followed Al-Azhar university ethical committee regulations and the patients consent was taken.

All patients and controls had been subjected to the following: full history taking and much more attention was paid towards age and sex, history of repeated abortion, previous history of venous or arterial thrombosis, history of manifestation suggestive autoimmune diseases (such as photosensitivity, oral ulcers, patchy hair loss, and Raynaud phenomenon ..etc). Clinical examination with special emphasis on manifestations of APS (Raynaud phenomenon, livedo reticularis, purpura ..etc).Systematic examination to assess manifestations of autoimmune diseases (arthritis, hepatosplenomegaly, serositis, cerebritis, carditis or nephritis). Laboratory investigations: Including Complete Blood Count (CBC), Lupus Anticoagulant (LA) and Anticardiolipin (aCL) antibody of IgG and/or IgM and Serum level of interleukin-6.

Statistical methodology:

Data entry and analysis were done using SPSS version 16. Data were presented as mean, SD, number and percentage. Chi-square test was used to compare qualitative data between the two groups of patients. Independent samples t-test was used to compare means of both groups. One Way Analysis of Variants (ANOVA) test for comparison between multiple groups with quantitative continuous variables. P-value considered significant when it was ≤ 0.05. Regression analysis was done and calculated for independent risk factors. Pearson’s and Spearman’s correlation coefficient were

used for correlating normal and non-parametric variables respectively.

The (+) sign was considered as indication for direct correlation i.e. increase frequency of independent lead to increase frequency of dependent & (-) sign as indication for inverse correlation i.e. increase frequency of independent lead to decrease frequency of dependent, also we consider values near to 1 as strong correlation & values near 0 as weak correlation.

RESULTS

Results of the study revealed that there was a statistically significant increase of arterial thrombosis in group B in comparison to group A (p value <0.001) and no statistically significant difference in group A in comparison to group B as regard to unexplained abortion, livedo reticularis, Raynaud phenomenon and purpuara. In addition, there was a statistically significant increase of IL6 in 1ry APS (group A), and 2ry APS (group B) in comparison to control group. On the other hand, there was no statistical significant difference between 1ry APS (group A) and 2ry APS (group B) as regard Lupus anticoagulant and Anti-cardiolipin Abs. As regard to CBC, WBCs in 1ry APS results showed a significant decrease of WBCs in 1ry APS in comparison to control group and a significant decrease of platelets in 1ry APS in comparison to control group but there is no statistically significant difference of Hb 1ry APS in comparison to control group **(Table 1)**.

Table (1): Statistical comparison between 1ry APS (group A) , 2ry APS (group B) and control (group C)

Groups / Variables	1ry APS (n = 30)		2ry APS (n = 30)		Control (n = 30)		P
	N	%	N	%	N	%	
Venous thrombosis	17	56.7%	23	76.7%	-	-	0.100
Arterial thrombosis	9	30%	24	80%	-	-	**<0.001**
Unexplained abortion	10	33.3%	12	40%	-	-	0.592
Livedo reticularis	10	33.3%	6	20%	-	-	0.243
Raynaud phenomenon	15	50%	10	33.3%	-	-	0.190
Purpuara	13	43.3%	13	43.3%	-	-	1.0
IL6	5.16 ± 2.28		5.42 ± 2.16		1.36 ± 0.6		**<0.001**
Lupus anticoagulant	28	93.3%	27	90%	-	-	0.640
Anticardiolipin Abs.	27	90%	26	86.7%	-	-	0.688
WBCS	4.96 ± 3.62		7.6 ± 4.13		8.68 ± 2.87		**<0.001**
Hb	13.45 ± 2.07		11.04 ± 3.9		12.9 ± 2.25		**<0.004**
Platelet	121.77 ± 43.08		151.1 ± 84.96		220.67 ± 62.42		**<0.001**

As regard CBC in 2ry APS; results showed no significant difference of WBCs in 2ry APS in comparison to 1ry APS but there was a significant increase of Hemoglobin in 1ry APS in comparison to 2ry group and statistically significant difference decrease of platelets 1ry APS in comparison to 2ry group **(Table 2)**.

Table (2): Statistical comparison between 1ry APS (group A) and 2ry APS (group B) as regard CBC

Groups / Variables	1ry APS (n = 30)	2ry APS (n = 30)	P
WBCS	4.96 ± 3.62	7.6 ± 4.13	0.245
Hb	13.45 ± 2.07	11.04 ± 3.9	**0.028**
Platelet	121.77 ± 43.08	151.1 ± 84.96	**0.001**

As regard correlation between IL6 versus different variables among 1ry APS there was positive correlation between IL6 levels and increase of Arterial thrombosis in patients with 1ry APS denoting that increased IL6 level is a risk factor for Arterial thrombosis in patients with 1ry APS. On the other hand, as regard correlation between IL6 versus different variables among 2ry APS there was no significant correlation between IL6 and different variables among patients of 2ry APS **(Table 3)**.

Table (3): Statistical correlation between IL6 versus different variables among 1ry APS (group A) and 2ry APS

Variables	IL6			
	R		P	
	1ry APS	2ry APS	1ry APS	2ry APS
Venous thrombosis	0.357	0.724	0.724	0.788
Arterial thrombosis	2.157	1.371	**0.040**	0.181
Unexplained abortion	0.240	0.203	0.812	0.840
Livedo reticularis	1.267	0.754	0.216	0.457
Raynaud phenomenon	0.904	0.457	0.374	0.406
Purpuara	0.582	0.137	0.565	0.892

R: sperman correlation

DISCUSSION

Primary antiphospholipid syndrome (PAPS) is a chronic immune-mediated disorder in which antibodies directed to phospholipid-binding proteins trigger a procoagulant and inflammatory state that leads to placental vascular complications and thrombotic events of various vascular beds. As opposed to secondary APS, an underlying autoimmune disease is not detected in PAPS *(Nuri et al., 2017).*

In the present study, as regard symptoms, there was a statistically significant increase of arterial thrombosis in group A in comparison to group B and no statistically significant differences in group A in comparison to group B as regard to unexplained abortion, livedo reticularis, Raynaud phenomenon and purpura. Our results were supported by study of *Bećarević and Ignjatović (2016)* as they reported that venous events were present in nine female and in four male patients. Deep venous thromboses (DVT) were present in seven female and in one male PAPS patients, while pulmonary emboli (PE) were registered in two female and in three male patients. Also, *Arantes et al. (2020)* demonstrated that among all

patients, 31% had arterial thrombosis and 35% had recurrent thrombosis. The median time elapsed from the last thrombotic event to enrollment for the study was 53.4 months.

Furthermore, *Tang et al. (2019)* revealed that there was a statistically significant difference among their studied groups as regard spontaneous abortion. *Hanouna et al. (2013)* reported that pregnancy complications are the other hallmark of APS. These complications include fetal death after 10 weeks gestation, premature birth due to severe preeclampsia or placental insufficiency, or embryonic losses (<10 weeks gestation).

The current study showed that as regard CBC there was a statistically significant decrease of WBCs in group A in comparison to group B and no statistically significant difference in group A in comparison to group B as regard to hemoglobin. WBCs in 1ry APS results showed a significant decrease in 1ry APS in comparison to control group and a significant decrease of platelets in 1ry APS in comparison to control group but there was no statistically significant difference of hemoglobin in 1ry APS in comparison to control group. CBC in 2ry APS results showed no significant difference of WBCs in 2ry APS in comparison to 1ry APS but there was a significant increase of Hemoglobin in 2ry APS in comparison to 1ry group and statistically significant difference decrease of platelets 2ry APS in comparison to 1ry group. However, *Artim-Esen et al. (2015)* revealed that thrombocytopenia and hemolytic anemia are hematological manifestations. Isolated thrombocytopenia is the most common hematologic abnormality in APS, occurring in about 30% of patients.

The present study showed a statistically significant increase in IL6 in 1ry APS (group A) and 2ry APS (group B) in comparison to control group with statistically significant difference between 1ry APS, 2ry APS (group B) and Control (group C). The study showed that IL 6 was a risk factor for arterial thrombosis in patients with 1ry APS. *Bećarević and Ignjatović (2016)* showed elevated IL-6 concentration which almost equally presented in female and male subgroups of patients. Increased levels of TNF-α and IL-6 have been consistently reported in patients with SLE and APS *(Manganelli and Capozzi, 2017)*. Our results were supported by study of *Arantes et al. (2020)* as they reported that patients with t-PAPS had an 8.6-fold increased levels of TNF-α, 90% increased levels of hs-CRP, 80% increased levels of IL-6 as compared with controls.

Cytokines (mainly IL-6) are inducers of hepatic production of acute-phase proteins, such as CRP. Some studies reported no association between the increased CRP and future events of venous thromboembolism (VTE), while other studies suggested that inflammation and increased CRP levels were involved in the development of VTE *(Zacho et al., 2010)*. Inflammation may interfere with various stages of hemostasis and some studies have found that proinflammatory cytokines (high levels of IL-6) were risk determinants for VTE, while others failed to confirm that finding *(Levi and van der Poll, 2010)*. VTE was associated with increased IL-6 levels and this association was independent of CRP in women with

secondary thrombotic episode and without any known disease (such as APS) that could predispose them to venous thrombosis *(Matos et al., 2011)*.

In the present study, Lupus anticoagulant and Anticardiolipin Abs. increased in 1ry APS and 2ry APS but without significant increase between studied groups. These results were supported by study of *Tang et al. (2019)* as they demonstrated that there was no statistically significant difference among their studied groups as regard Lupus anticoagulant and Anticardiolipin Abs. Furthermore, *Gustafsson et al. (2015)* reported that in SLE, 30%–40% of patients are positive for aPL; when each aPL is investigated individually, the prevalence of a positive LA test and aCL varies between 11%–30% and 17%–40%, respectively.

The current study showed that there was positive correlation between IL6 levels and increase of Arterial thrombosis in patients with 1ry APS denoting that increased IL6 level is a risk factor for Arterial thrombosis in patients with 1ry APS.

TNF-αand IL-6 is cytokines released by macrophages and involved in local and systemic inflammation. IL-6 also stimulates hepatocytes to release acute phase proteins, such as CRP. In vitro studies demonstrated that antiphospholipid antibodies, in particular anti-beta2 glycoprotein 1, are capable of binding to monocytes and inducing the release of both TNF-α and TF *(Rauch et al., 2018)*. In a study conducted by *Palli et al., (2019),* increased levels of TNF-α and IL-6 have been consistently reported in patients with APS and an enhanced type I IFN gene signature has been demonstrated in PAPS patients with thrombosis. Therefore, our findings provide additional evidence for an association between t-PAPS and a proinflammatory state.

CONCLUSION

The use of selective IL6 inhibitors in those patients may help to reduce inflammation and may provide a potential preventive measure for prothrombotic complications.

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معدل الانترلوكين 6 فى متلازمة الفوسفوليبيد الأولية

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خلفيـــة البحـــث: تعـــد متلازمـــة الفوســـفوليبد اضـــطرابا فـــي جهـــاز المناعـــة الـــذاتي والـــذي قـــد يـــؤدي إلـــي الوفـــاه أو مضـــاعفات متعـــدده. وتظهـــر العديـــد مـــن الســـيتوكينات فـــي متلازمه الفوسفوليبد ويعد الانترليوكن ٦ واحدة من هذه السيتوكينات.

الهـــدف مـــن البحـــث: تقيـــيم مســـتوى للإنترلـــوكين ٦ وعلاقتـــه بمخـــاطر التخثـــر لـــدى المرضى الذين يعانون من متلازمة الفوسفوليبد الأولية.

المرضـــي وطـــرق البحـــث: أجريـــت هـــذه الدراســـة علـــى ســـتين مريضـــاً يعـــانون مـــن متلازمـــة الفوســـفوليبد وثلاثـــين متطوعـــاً أصـــحاء كعنصـــر تحكـــم وقـــد تـــم اختيـــارهم مـــن العيـــادات الداخليـــة والعيـــادات الخارجيـــة بقســـم الامـــراض الباطنيـــة ووحـــدة المناعـــة مـــن مستشـــفيات جامعـــة الأزهـــر (مستشـــفى الحســـين ودميـــاط الجديـــدة ومستشـــفي جامعـــة الأزهـــر)، فـــي الفتـــرة مـــن نـــوفمبر 2019 إلـــى ديســـمبر 2019. كمـــا تـــم تقســـيمهم إلـــى المجموعـــات المتســـاوية: المجموعـــة (أ) يعـــانون مـــن متلازمـــه الفوســـفوليبد الأوليـــه، والمجموعـــة (ب) يعـــانون مـــن متلازمـــه الفوســـفوليبد الثانويـــة، والمجموعـــة (ج) الأصـــحاء كمجموعـــة تحكـــم. وقـــد تـــم إخضـــاع جميـــع المرضـــي للتـــاريخ المرضـــى والفحص الاكلينيكي والفحوصات الاساسيه مع تقييم معدل الانترليوكن 6.

نتـــائج البحـــث: كانـــت هنـــاك زيـــادة ذات دلالـــة إحصـــائية فـــي الانترليـــوكن 6 بـــين المرضـــى الـــذين يعـــانون مـــن متلازمـــة الفوســـفوليبد الأوليـــة وكـــذلك المرضـــى الـــذين يعـــانون مـــن متلازمـــة الفوســـفوليبد الثانويـــه وقـــد كـــان العـــرض الأكثـــر شـــيوعًا بـــين المرضـــي الـــذين تمـــت دراســـتهم فـــي متلازمـــة الفوســـفوليبد الاوليـــة هـــو الجلطـــة الوريديـــة (17 ٪), والجلطـــة الشـــريانية (9 ٪) والإجهـــاض غيـــر معـــروف الســـبب (10%). أمـــا فيمـــا يتعلـــق بمتلازمـــة الفوســـفوليبد الثانويـــة فقـــد كـــان العـــرض الأكثـــر شـــيوعًا بـــين المرضـــي الخاضـــعين للدراســـة هـــو الجلطـــة الوريديـــة (23٪) والجلطـــة الشـــريانية (24٪), والإجهـــاض غيـــر المبـــرر (12٪). وبالمقارنـــة بـــين المجموعـــات المدروســـة

فيما يتعلق بمتوسط إنترلوكين -6 كان هناك فرقا كبيرا بين متلازمه الفوسفوليبد الاولية والثانوية والمجموعات الضابطة. كما أظهرت هذه الدراسة أن هناك علاقة إيجابية بين إنترلوكين -6 مع تجلط الدم الشرياني بين المرضى المصابين بمتلازمه الفوسفوليبد الاولية، ولم يتم الكشف عن أي ارتباط بين إنترلوكين -6 وتجلط الشرايين بين المرضى المصابين بمتلازمه الفوسفوليبد الثانويه فيما يتعلق بالعلاقة بين التجلط الوريدي ومتوسط إنترلوكين -6. في المرضى الذين يعانون من متلازمه الفوسفوليبد الاوليه والثانويه لم يكن هناك ارتباطات إيجابية ذات دلالة إحصائية فيما يتعلق إنترلوكين -6.

الخلاصة: أثبتت الدراسة ارتفاع معدل الانترليوكن 6 في المرضى الذين يعانون من متلازمة الفوسفوليبد الاولية وتبين أن ارتفاع الانترليوكن 6 يرتبط بشكل إيجابي بتخثر الشرايين.

الكلمات الدالة: الانترليوكن 6, متلازمة الفوسفوليبد, السيتوكين.