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ORIGINAL ARTICLE

Primary Antiphospholipid Syndrome: A Hidden Predisposing Factor for Retinal Vein Occlusion and Choroidal Neovascular Membrane Formation Among Young Population

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Abstract

Background & Objectives: Antiphospholipid syndrome can lead to variable systemic and ophthalmic manifestations. The study aims to establish the relationship between retinal vein occlusion (RVO) or choroidal neovascular membrane (CNVM) with Antiphospholipid Syndrome (APS).

Methods: A multicentric prospective cross-sectional study was carried out in three major eye centers in Bahrain that included The Eye Infirmary, Bahrain Royal Hospital, and King Hamad University Hospital.

All young patients aging from 35 to 50 years, presenting with either RVO or CNVM and not known to have any underlying systemic disease were included in the study. Antiphospholipid confirmatory tests and coagulation profiles were done for all patients.

Results: Total number of fourteen eyes of ten patients were enrolled in the study. Six patients had RVO, three out of them had central retinal vein occlusion (CRVO) and three had branch retinal vein occlusion (BRVO). Four patients had bilateral CNVM (total of 8 eyes). All patients recorded high activated partial thromboplastin time (aPTT) readings, six out of ten patients were labeled as primary APS, four of them had positive anti-cardiolipin antibodies and the other two patients were positive for plasma lupus anticoagulant.

Conclusion: APS should be considered as an etiological factor in all cases of retinal vein occlusion and choroidal neovascular membrane affecting young otherwise healthy individuals. In this study, 60% of patients who fit the inclusion criteria were labeled as primary APS patients. Timely investigations and treatment in these cases can prevent major catastrophic thrombotic events which may involve any system or organ in the body.

Keywords: Antiphospholipid syndrome, Blood coagulation tests, Eye, Lupus coagulation inhibitor, Retinal vein occlusion

Introduction

Retinal vein occlusion (RVO) and choroidal neovascular membrane (CNVM) are two ocular disorders seen more often in the older population; this can be attributed to the comorbidities that are more prevalent in the older age group like diabetes, hypertension, and dyslipidemia that affects their vascular integrity and health.[1] When any of these ocular pathologies are encountered in a young healthy individual without any known systemic risk factors, this leads to a high index of suspicion for the possibility of underlying systemic disease.

Antiphospholipid syndrome (APS) is an acquired thrombophilic disease causing arterial or venous clotting disorder affecting any part of the body and leading to various complications, ranging from mild symptoms to permanent disability or organ failure, recurrent miscarriage, and even death.[2,3] Up to 80% of APS patients can have ocular involvement, many cases can have it as a first manifestation which can range from mild symptoms such as dry eye to sight-threatening conditions and blindness.[4-6]

APS could be either primary or secondary to other rheumatic diseases such as systemic lupus erythematosus (SLE).[7] The relatively high incidence of serious ocular complications in APS makes the role of ophthalmologists crucial as early detectors in the case of primary APS. The study aims to focus on two potentially vision-threatening conditions; RVO and macular CNVM in young healthy individuals without any known risk factors or chronic diseases.

The study will help in assessing the incidence of APS among young individuals presenting with RVO or CNVM.

This will lead to early diagnosis and treatment of APS, which will decrease the risk of more advanced and life-threatening complications.

Materials and Methods

This is a multicentric prospective cross-sectional study. Any patient presenting to ophthalmology clinic in King Hamad university hospital, The Eye Infirmary, and Bahrain Royal Hospital with a complaint of blurriness of vision secondary to either RVO or CNVM during the period of 2016-2019 was included in this study.

This prospective cross-sectional study was approved by the ethics and research department in King Hamad University hospital, reference number: KHUH/Research/No/ 188.2017.

Patients falling in the age group 35-50 years old with confirmed RVO or CNVM were included.

Patients with predisposing risk factors such as diabetes, hypertension, dyslipidemia, smoking, or already diagnosed with secondary APS were excluded from the study.

The total number of patients fitting the criteria was 10 with 4 patients having both eyes affected, hence a total of 14 eyes were enrolled in the study (Table 1).

Table 1: Demographic data of the patients

Patient No	Eye problem	Gender	Age (years)
1	RVO (unilateral)	Female	35
2	RVO (unilateral)	Female	41
3	RVO (unilateral)	Male	36
4	RVO (unilateral)	Male	32
5	RVO (unilateral)	Male	44
6	RVO (unilateral)	Male	45
7	CNVM (bilateral)	Female	32
8	CNVM (bilateral)	Male	49
9	CNVM (bilateral)	Male	37
10	CNVM (bilateral)	Male	40

Visual acuity slit-lamp examination and fundoscopy were done for all patients. Diagnosis of RVO or CNVM was confirmed by Optical Coherence Tomography (OCT) and Fundus Fluorescence Angiography (FFA). Vital signs and blood investigations including random blood sugar, Hemoglobin A1c (HbA1c), and lipid profile were done to rule out any underlying systemic diseases.

Informed consent was obtained from the patients who fit the criteria before doing the laboratory investigations.

Patients tested for activated partial thromboplastin time (APTT), values > 42.9 seconds were considered as high. APS antibodies were considered positive in the following scenarios; positive titer of lupus anticoagulant antibody (LA), Anticardiolipin (aCL) Immunoglobulin M (IgM) isotype in serum or plasma titer higher than 40 MPL, Anticardiolipin

(aCL) Immunoglobulin G (IgG) isotype in serum or plasma titer higher than 40 IgG phospholipid (GPL) units, Beta-2 Glycoprotein 1 (beta-2 GP1) IgM antibody titer higher than 40 U/mL or Beta-2 Glycoprotein 1 (beta-2 GP1) IgG antibody titer higher than 40 U/mL (Table 2).[8]

Table 2: Antiphospholipid Syndrome Antiphospho lipid Syndrome diagnostic criteria

LA	Positive titre
aCL IgM	> 40 MPL
aCL IgG	> 40 GPL
beta-2 GP1 IgM	> 40 U/mL
beta-2 GP1 IgG	> 40 U/mL

One-way ANOVA and Descriptive statistical tests were performed using SPSS version 19.

Results

The mean age of the patients was 39.1 ± 5.70 (range of 32 - 49 years). The demographic data for the patients are depicted in Table 1.

Six patients with unilateral RVO (total six eyes), two of which were females and four males. The male to female ratio in RVO patients was approximately 1:3. Three patients had BRVO (50 %) and the other three have CRVO (50%). (Figures 1 A & B)

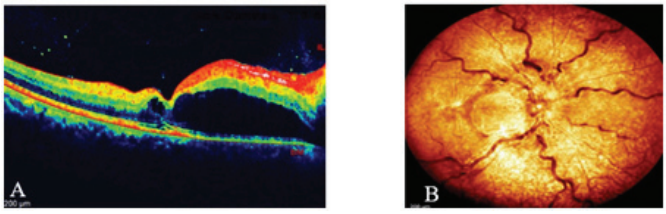

Figure 1: A 33-year-old female with right eye a typical Central retinal vein occlusion (CRVO), high APTT and positive cardiolipin, (A) Optical coherence tomography (OCT) macula showing increased macular thickness. (B) Fundus photo showing disc edema

Four patients had bilateral CNVM (total of eight eyes), one female and 3 males. The female to male ratio in CNVM patients was 1:4 (Figure 2).

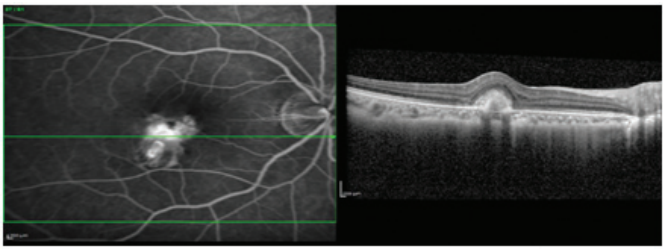

Figure 2: A 30-year-old female, with high APTT and lupus antibody positive showing choroidal neovascular membrane (CNVM), on the right side: Fluorescence angiography showing macular hyper fluorescence, on the left side: corresponding optical coherence tomography (OCT) for the same lesion in right sided image

Four patients had CNVM (8 eyes), three patients had CRVO (3 eyes) and three patients had BRVO (3 eyes).

Overall, four females and ten males were enrolled in the study, with ages ranging from 32 to 49. The distribution of the disease among both gender and age is illustrated in table 3 with a P value of 0.84.

All patients have high APTT readings, six out of ten patients (60%) were positive for APS antibodies and were labeled as primary APS. Forty percent (40%) of patients who fit the criteria showed only high APTT, but no antibodies were detected in their serology.

Out of the positive patients, four were positive for anti-cardiolipin IgG (66.66%) and two were positive for plasma lupus anticoagulant (33.33%) (Figure 2).

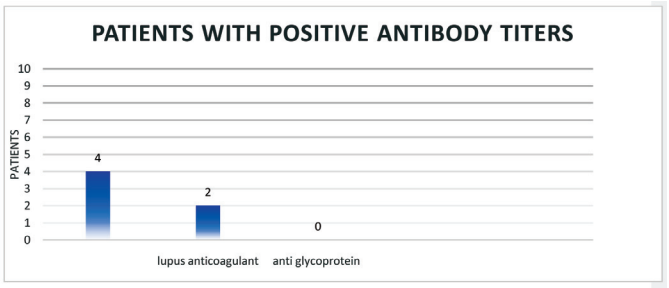

Figure 3: Number of patients with positive antiphospholipid titers

Table 3: Depicted the ANOVA test comparing the disease with both age and gender

		N	Mean	Std. Devi	Std. Error	95% Confidence Interval for Mean		df	F	Sig.
						Lower	Upper			
Age	RVO	6	38.83	5.26	2.15	33.30	44.36	1	0.041	0.84
	CNVM	8	39.50	6.61	2.33	33.97	45.02	12		
	Total	14	39.21	5.86	1.56	35.83	42.59	13		
Sex	RVO	6	1.33	.51	.21	.791	1.87	1	0.101	0.75
	CNVM	8	1.25	.46	.16	.863	1.63	12		
	Total	14	1.28	.46	.12	1.015	1.55	13		

Discussion

Antiphospholipid syndrome (APS) is an autoimmune disorder of the homeostatic system. It is characterized by the presence of antiphospholipid antibodies with one of the following clinical manifestations; namely arterial or venous thrombosis or repetitive fetal loss.[2,3] It was first described by Hughes, *et al*. in 1983, since then it is increasingly getting attention worldwide as its prevalence has reached up to 50 cases per 100,000 population.[9,10] In APS, autoantibodies are produced against a variety of phospholipids and phospholipid-binding proteins, these antibodies include anticardiolipin antibodies, b-2-glycoprotein-1 antibodies, and lupus anticoagulant.[8]

APS can affect blood vessels in all vascular segments in the human body and it's characterized by hypercoagulability-related diverse symptoms. Ocular manifestations are prevalent in APS.[4] Although the most common ocular manifestation in APS is retinal vascular occlusion, many other ocular manifestations have been documented, and it can affect any part of the Human eye including anterior and posterior segments.

APS can have anterior segment manifestations such as dry eye syndrome, punctate epithelial keratopathies, scleritis, uveitis.[11-13] Posterior segment manifestations commonly include retinal vascular occlusions and formation of macular choroidal neovascular membranes.[13-15] Either Retinal vascular occlusion or macular choroidal vascular membrane can cause permanent visual loss.[16] Nonarteritic anterior ischemic optic neuropathy, retrobulbar neuritis, and frosted branch angitis are also reported in primary APS.[18-20]

Human retina receives blood supply by two main circulations, retinal and choroidal blood vessels.[21] Systemic diseases affecting the vascular system can affect the eye by causing damage to retinal and/or choroidal blood supply. Retinal blood circulation disease can present as retinal vein occlusion which can be in form of BRVO or more profound as CRVO. The arterial system can also be affected to a lesser extent, and this can present in a form of central retinal artery occlusion (CRAO) and less commonly cilioretinal artery occlusion.[12-1] On rare occasions, both arterial and venous systems can be involved at the same time. [22] Choroidal system is frequently damaged by vascular diseases as well, this damage results in ischemia that stimulate the formation of choroidal neovascularization that leads to secondary exudative changes.[16] Both retinal and choroidal involvements are considered serious sight-threatening complications, with the latter being more guarded in terms of visual outcome and prognosis.

In general populations vascular complications tend to be more frequent in older populations, this can be attributed to the fact that diabetes, hypertension, and dyslipidemia are more common in this age group. It is uncommon to encounter those presentations in a patient who is younger than 50 years. Hence, RVO or CNVM in a patient younger than 50 years tends to be an alarming sign that a serious underlying systemic condition might be blameworthy.[1] Many studies highlighted the association between antiphospholipid syndrome and pathology of CRVO and CNVM in young age groups in the absence of other risk factors.[12-14]

Antiphospholipid syndrome complications can be

serious and multisystemic; it is highly linked to recurrent abortion, stillbirth, and preeclampsia.[3] APS can cause significant morbidity and mortality as its directly linked to increased risk of pulmonary hypertension, pulmonary embolism, deep venous thrombosis, stroke, coronary artery disease, and cardiac embolisms.[23] Those complications if not treated promptly and appropriately can be life-threatening.

Treatment is mainly directed towards preventing arterial and venous thrombosis which is mainly achieved by anticoagulants such as heparin or warfarin in addition to antiplatelet such as aspirin. In acute severe cases, heparin in conjunction with high-dose corticosteroids and plasma exchange can be the optimal choice. New proposed treatment options that are not based on anti-coagulation are found to be beneficial like rituximab, autologous stem cell transplantation, and hydroxychloroquine.[24]

Conclusion

By knowing that antiphospholipid syndrome can predispose to sight-threatening complications such as RVO and CNVM, all young individuals presenting to the ophthalmologist with those complications should be screened for APS. Many pieces of research have documented that APS can present initially with ocular complications before systemic complications. Identifying APS patients early in the disease course and treating them prophylactically before developing systemic complications can save their lives, improve the quality of their life, and reduce the burden on the economy as those complications demand a lot of resources, expensive and prolonged treatment, and rehabilitation.

To have a wider view of the disease, we recommend that patients who are newly diagnosed with secondary APS should undergo baseline ophthalmic examination. This will help to identify the incidence of eye complications in APS patients. This will also help in the early detection of any eye complication and saving the vision.

This might lead to changing the guidelines for the diagnosis and treatment of APS patients in the future.

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Conflicts of Interest

None.

Competing Interest

None.

Sponsorship

None.

Ethical Approval

Approved by the Research and Ethics Committee, King Hamad University Hospital, Bahrain.

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