

Antiphospholipid syndrome and retinal vein occlusion in adults

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متلازمة مضادات الفوسفوليبيد وانسداد الوريد الشبكي بين البالغين

راوي منير معروف، رشيد حمدي، ناجية جميلي، محمد غربال، فافاني بالحاج حميدة، تهامي محبوب

الخلاصة: قد يكون لأضداد الفوسفوليبيدات دور هام في إحداث انسداد الأوعية الشبكية، وقد قام الباحثون باستقصاء معدل انتشار هذه الأضداد في 33 مريضاً بانسداد الشرايين والأوردة الشبكية و80 من الشواهد. وقد بلغ معدل الانتشار بين المرضى 33% وبين الشواهد 5%. وأظهر الفحص العيني وتصوير الأوعية بالفلوريسين أن الانسداد كان ناجماً عن أحداث نقص التروية. وقد شخّصت متلازمة مضادات الفوسفوليبيد لدى 11 مريضاً، تمت معالجة 9 مرضى منهم بنجاح بالتخثير بالليزر وبالأدوية المضادة للتخثر والمضادة لتكدّس الصفائح، في حين كانت معالجة مريضين بهذه المتلازمة المصحوبة بالمقاومة للبروتين سي المفعل دون نتائج مشجعة. وتشير النتائج التي توصل إليها الباحثون إلى وجود ترابط بين متلازمة مضادات الفوسفوليبيد وانسداد الأوردة الشبكية، ولذلك فإنهم يوصون بإجراء بحوث منهجية حول دور أضداد الفوسفوليبيدات في الانسداد غير المفسّر المنشأ وحول المعالجة بالتخثير بالليزر وبالأدوية المضادة للتخثر والمضادة لتكدّس على المدى الطويل.

ABSTRACT Antiphospholipid antibodies may play an important role in the pathogenesis of retinal vascular occlusions; therefore, we investigated the prevalence among 33 patients with retinal vein and artery occlusions and 80 controls. Prevalence was 33% and 5% respectively. Ophthalmic examination and fluorescein angiography showed that occlusions were due to ischaemic events. The 11 patients were diagnosed with antiphospholipid syndrome: 9 patients were treated successfully with laser photocoagulation and anticoagulant and anti-aggregant therapy. Two patients with antiphospholipid antibodies associated with resistance to activated protein C had unfavourable outcomes. Our results suggest a correlation between antiphospholipid syndrome and retinal vein occlusions; we recommend a systematic search for antiphospholipid antibodies in occlusions of unexplained origin and laser photocoagulation treatment and long-term oral anticoagulant and anti-aggregant therapy.

Le syndrome des antiphospholipides et l'occlusion veineuse rétinienne chez l'adulte

RÉSUMÉ Les antiphospholipides peuvent jouer un rôle important dans la pathogénèse des occlusions vasculaires rétiniennes ; nous avons donc étudié la prévalence chez 33 patients atteints d'occlusions veineuses et artérielles rétiniennes et 80 témoins. La prévalence s'élevait à 33 % et 5 % respectivement. L'examen ophtalmologique et l'angiographie fluorescéinique ont montré que les occlusions étaient dues à des événements ischémiques. Le syndrome des antiphospholipides a été diagnostiqué chez 11 patients : neuf patients ont été traités avec succès par photocoagulation au laser associant un traitement anticoagulant et antiagrégant. Deux patients présentant des anticorps antiphospholipides associés à une résistance à la protéine C activée ont eu une issue défavorable. Nos résultats semblent indiquer une corrélation entre le syndrome des antiphospholipides et les occlusions veineuses rétiniennes ; nous recommandons une recherche systématique des anticorps antiphospholipides dans les occlusions d'origine inexpliquée et un traitement par photocoagulation au laser et un traitement anticoagulant et antiagrégant de longue durée.

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Introduction

Antiphospholipid antibodies are a heterogeneous family of antibodies directed to plasma protein co-factors bound to anionic phospholipids. The clinical relevance of antiphospholipid antibodies derives from the association with venous and arterial thrombosis, recurrent abortions and thrombocytopenia [1]. Antiphospholipid antibodies include lupus anticoagulant and anticardiolipin antibodies [2,3]. This association has been termed the antiphospholipid syndrome (APS), which may occur alone (primary APS) or in the setting of an underlying disease, mainly systemic lupus erythematosus (SLE) [4–7].

Hypercoagulable states, including a variety of disorders such as reduced levels of antithrombin, protein C, protein S or presence of antiphospholipid antibodies, are common in patients with retinal vein occlusions and may contribute to the etiology of the disease [8].

In particular, retinal vascular occlusions in patients with primary APS, i.e. with antiphospholipid antibodies but with no other conventional risk factors, result from thrombus formation in either the retinal vein, artery or both [9–12].

We investigated the prevalence of antiphospholipid antibodies in a group of 33 patients with retinal vein occlusion and in 80 normal controls. Whether antiphospholipid antibodies included lupus anticoagulant, anticardiolipin antibodies or both was also investigated. This study aimed to assess the relationship between the occurrence of antiphospholipid antibodies in primary APS and occlusive retinal vascular events.

Methods

From January–December 2002, 33 patients (14 men and 19 women, mean age 37 years

and age range 22–63 years) with retinal vein (29) or artery (4) occlusions were selected from the Department of Ophthalmology of the Farhat Hached Hospital, Sousse, Tunisia. Exclusion criteria were diabetes, hypertension, hypercholesterolaemia and hypertriglyceridaemia. We used 80 normal controls from among healthy blood donors at the Centre Régional de Transfusion Sanguine of Farhat Hached Hospital. Informed consent was obtained from patients and controls prior to their participation in our study.

Patients were examined clinically. A questionnaire was administered before patients underwent ophthalmologic examination and retinal fluorescein angiography.

Biological assays for cholesterol and triglycerides were performed. Antinuclear antibodies were investigated with standardized enzyme-linked immunosorbent assay (ELISA).

Screening studies for APS included assays for anticardiolipin antibodies and lupus anticoagulant. Anticardiolipin antibodies (IgG and IgM isotypes) were also determined by ELISA assay (Diagnostica Stago, Asnières, France). Lupus anticoagulant was assayed with clotting techniques. Anticardiolipin antibodies and lupus anticoagulant were measured 8 weeks later.

We also screened for abnormalities in the coagulation process. Activated partial thromboplastin time and kaolin clotting time tests were performed. The levels of protein C and protein S were determined by ELISA assay (Diagnostica Stago, Asnières, France). Antithrombin III level was evaluated by colorimetric assay (Asserachrom, Diagnostica Stago, Asnières, France) and levels of factors VIIIc and XI were determined with clotting assays (Diagnostica Stago, Asnières, France). Factor V Leiden was investigated through the evaluation of the activated protein C–sensitivity ratio

(Accelerimat, bioMérieux, Marcy l'Etoile, France). Genetic analysis of factor V Leiden mutation was performed as previously described [13].

Chi-squared test was used to compare the patient and control groups.

Results

All patients underwent fundus fluorescein angiography and ophthalmologic examination. Almost all suffered from retinal vein occlusions (29 of 33 patients); the occlusive events primarily involved the central (9 patients) and the temporal (8 patients) veins. Only 4 patients had artery occlusions (Table 1). The prevalence of antiphospholipid antibodies in the study group was 33% (11 of 33 patients) while in the control group it was 5% (4 of 80). This difference was statistically significant ($\chi^2 = 16.29$, $P < 0.001$).

All patients with antiphospholipid antibodies had retinal vein occlusions, particularly temporal vein occlusions (5 of 11 patients). Only 1 patient with antiphospholipid antibodies had a central vein occlusion. None of the patients with artery occlusions tested positive for any of the assays.

In the study group 2 patients were positive for IgG-anticardiolipin antibodies, 3 patients for IgM-anticardiolipin antibodies and 1 patient for both isotypes IgG and IgM-anticardiolipin antibodies. The 5 remaining patients were negative for anticardiolipin antibodies but showed positivity for lupus anticoagulant (Table 1). Two patients had associated protein C resistance. All patients were negative for antinuclear antibodies. No deficiency in antithrombin III, protein C or protein S was found. Factors VIII and XI levels were within normal.

Table 1 Presence of anticardiolipin antibodies, lupus anticoagulant and factor V Leiden among the 11 retinal vein occlusion patients testing positive for antiphospholipid antibodies

Measurand	No.
Anticardiolipin antibodies	6 ^a
IgG	2
IgM	3
IgG and IgM	1
Lupus anticoagulant	5
Associated factor V Leiden	2
Antinuclear antibodies	0

Discussion

The etiology of retinal vein occlusion is still not well understood although thrombosis does occur histologically. Hypercoagulable states seem to be common in patients with retinal vein occlusions [8]. The presence of antiphospholipid antibodies in APS is likely to generate a hypercoagulable state such as to cause thrombosis to occur [1]. It is known that antiphospholipid antibodies impair the metabolism of arachidonic acid in endothelial cells and platelets causing the inhibition of prostaglandin I₂ (PGI₂) production by endothelial cells and activation of platelets through stimulating thromboxane A₂ generation [14,15]. Furthermore, antiphospholipid antibodies inhibit protein C and protein S, preventing coagulation factors Va and VIIa from inactivation [16,17]. Among other implications of the antiphospholipid antibodies syndrome is an increase in tissular factor release and in plasminogen activator inhibitor level. These implications could make it possible for thrombosis to occur even in veins or arteries, although

most vascular occlusions (81%) were found to affect venous vessels in a recent study [11].

Elevated levels of anticardiolipin antibodies have recently been associated with acute vascular occlusions of the eye although their role remains unclear [12,18–21]. Of 33 patients with retinal vascular occlusions, 11 (33%) were diagnosed with APS. They possibly had primary APS without any underlying immune disorder like lupus erythematosus because each was negative for antinuclear antibodies. None of our patients, however, was investigated for other possible immune disorders. It is noteworthy that 9 of the 11 patients had no other conventional risk for thrombosis, whereas the presence of antiphospholipid antibodies was associated with resistance to activated protein C for the 2 others.

The high prevalence of antiphospholipid antibodies in our study indicates that antiphospholipid antibodies may play an important role in the pathogenesis of retinal vein occlusions and thus may represent a risk factor of importance in the etiology of the disease. This may also suggest the necessity of screening for antiphospholipid antibodies in such patients. Furthermore, in our study group, the prevalence of antiphospholipid antibodies seemed to be related to retinal vein occlusions mainly involving the temporal vein and not to artery vein occlusions. This warrants further investigation. It should be noted that the role of antiphospholipid antibodies in retinal vein occlusion is still controversial. Our results provide more support for such a role of antiphospholipid antibodies in the pathogenesis of this disease.

Our results (33% prevalence of antiphospholipid antibodies in patients with retinal vascular occlusions) were dissimilar from studies that identified lower preva-

lences of 5%, 7.5% and 9% respectively among patients with primary APS [18,9,12]; however, in the two latter studies, these levels could have been 22.5% and 22% if antiphospholipid antibodies were associated with lupus erythematosus, the elevation of circulating immune complexes or complement deficiencies respectively [9,12]. Our results nevertheless indicate higher prevalence of antiphospholipid antibodies in retinal vein occlusions than the results of these authors. It should be noted that our study is the first of its kind in Tunisia and that a cohort study among the Tunisian population is needed.

In our study, all patients with antiphospholipid antibodies except 2 were treated successfully with laser photocoagulation and anticoagulant and anti-aggregant therapy (acenocoumarol, to get the patient's international normalized ratio to 2–4, and lysine acetylsalicylate, 250 mg per day) [22]. The 2 exceptions had associated resistance to activated protein C with the presence of antiphospholipid antibodies and experienced unfavourable developments. One had an occlusive event in the second eye and the other became blind even though therapy was provided.

In retinal vascular occlusions of unexplained origin, antiphospholipid antibodies may play an important role in pathogenesis. Detecting these antibodies in the serum of patients with retinal vascular occlusions may help to determine the appropriate treatment. The high prevalence of anticardiolipin antibodies in these patients who are free of conventional risk factors leads us to recommend a systematic search for specific antiphospholipid antibodies for them. This should be part of a treatment combining laser photocoagulation, and long-term anti-aggregant and oral anticoagulant therapy [19].

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Correction

Screening for congenital hypothyroidism in the Islamic Republic of Iran: strategies, obstacles and future perspectives A. Ordookhani, P. Mirmiran, R. Hajipour, M. Hedayati and F. Azizi. *Eastern Mediterranean Health Journal*, 2002, Vol. 8 Nos 4/5, pages 480-9.

The title of the French abstract should read:

Dépistage de l'hypothyroïdie congénitale en République islamique d'Iran : stratégies, obstacles et perspectives futures and hypothyroïdie should replace hyperthyroïdie throughout the text of the abstract.

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