HYPERCOAGULABLE WORKUP IN OPHTHALMOLOGY. WHEN AND WHAT?

ESTUDIOS DE HIPERCOAGULABILIDAD EN OFTALMOLOGÍA. ¿QUÉ PEDIR Y CUÁNDO?

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ABSTRACT

Most ophthalmologic disorders secondary to hypercoagulable state are due to the confluence of congenital and acquired factors. A systematic workup is mandatory.

Most of congenital coagulation disorders cause venous thrombosis and are inherited autosomally. In order of frequency these are factor V Leiden mutation (activated protein C resistance), G20210A mutation of the prothrombin gen and protein C, protein S, and antithrombin III deficiencies. Sickle cell anemia can determine arterial and venous thrombosis.

In relation with arterial occlusion, the markers most frequently involved are homocysteine fasting levels and the markers of antiphospholipid antibody syndrome. Both of them can also determine venous thrombosis.

Several acquired factors can lead to hypercoagulable state, especially hyperhomocysteinemia, antiphospholipid antibody syndrome, hepatic disease, alcohol and tobacco intake, oral contraceptives, immobilization, surgeries and malignancies.

In central venous occlusion is only necessary to rule out hyperhomocysteinemia and antiphospholipid antibody syndrome in young patients without known risk factors.

RESUMEN

La mayoría de los trastornos oftalmológicos secundarios a hipercoagulabilidad se deben a la confluencia de factores congénitos y adquiridos. Dada la multitud de test diagnósticos existentes se hace preciso una sistematización de la solicitud de los mismos.

La mayoría de los trastornos congénitos de la coagulación producen trombosis venosas y son de herencia autosómica dominante. Los más frecuentes son por este orden la resistencia a la proteína C activada (Factor V Leiden), la mutación del gen de la protrombina (G20210A), déficit de proteína C proteína S y de antitrombina III. La anemia de células falciformes puede acompañarse de fenómenos oclusivos arteriales y venosos.

Respecto a las trombosis arteriales, los marcadores implicados más frecuentemente son los niveles de homocisteína en ayunas y los del síndrome de anticuerpos antifosfolípidos, aunque ambos producen oclusiones venosas fundamentalmente.

Diversos factores adquiridos pueden producir estados hipercoagulables. Dentro de las entidades más frecuentes destacamos la hiperhomocisteínemia y el síndrome de anticuerpos antifosfolípidos, sin olvidar múltiples circunstancias como patología hepática, ingesta de alcohol, tabaco, anticonceptivos orales, inmovilización, cirugía y enfermedades mielo-
In central artery occlusion, hypercoagulable work-up is only recommended for patients less than 50 years-old with unknown emboli source. In this cases protein C, protein S, and antithrombin III deficiencies, homocystein, sickle cell disease and antiphospholipid antibody syndrome will ruled out. In non arteritic ischemic optic neuropathy hypercoagulable work up is not necessary.

In amaurosis fugax without known emboli source, it is recommended to rule out etiologies of arterial occlusion, especially antithrombin III deficiencies, homocystein, sickle cell disease and antiphospholipid antibody syndrome (Arch Soc Esp Oftalmol 2009; 84: 325-332).

**Key words:** Hypercoagulability, retinal venous occlusion, central retinal artery occlusion, hyperviscosity.

**CONGENITAL DISORDERS**

All hypercoagulability disorders (Table I) predispose to venous thrombosis, although some can also predispose to arterial thrombosis (mutation of the prothrombin G20210A gene, antithrombin III deficit, sticky platelet syndrome and sickle cell anemia) (1). The majority of these disorders exhibit autosomic dominant inheritance (AD).

**Resistance to activated protein C (Leiden Factor V)**

This resistance appears in 5% of the white population, reaching 20% in Sweden and the Middle East. Inheritance is AD. It has been identified in 20% of subjects with a first thrombosis event and in 50% with familial thrombosis. In 95% of cases, the defect is associated to the substitution of argynine by glycine in position 506 of the Factor V molecule, giving rise to a resistance to activated protein C (APC).

**Mutation of the prothrombin gene (G20210A)**

This mutation exists in 1-4% of the general population and is due to a mutation (G for A) in nucleotide 20210 of the prothrombin gene, associated to an increase in prothrombin plasmatic concentrations. It increases 3 to 5 times the risk of venous thrombosis and is greater in individuals who also carry Leiden’s factor V (2). It has also been associated to ahigher risk of cerebro-vascular event, heart attack (arterial involvement) and retinal central vein occlusion (3).
Protein C Deficit (0.15-0.5% of the general population, AD inheritance)

15% of subjects with protein C deficit which developed with thrombosis also exhibit APC resistance. Anticumarins can induce skin necrosis.

Protein S Deficit (0.7% of the general population, AD inheritance)

As in the previous case, this defect is found in heterozygotic form in 1-3% of subjects with venous thrombosis. Three types are differentiated:

– Type I (classic form) exhibiting both a quantitative and qualitative deficit
– Type II only exhibiting a functional alteration of the protein
– Type III in which free protein S is diminished even though the total values for protein S can be normal.

Antithrombin III Deficit (0.17% of the general population, AD inheritance)

Heterozygotic individuals have functional activity rates between 30 and 60% of normal values, whereas the homozygotic state is in theory incompatible with life. A relation of this condition is the mutation of the joining place of antithrombin III with heparin. In this case, mutated antithrombin is unable to join heparin, thus reducing its anticoagulant efficiency and that of other enzymes closer to the coagulation cascade. The result is a phenotype which tends to arterial and venous thrombosis.

Dysfibrogenemia

A rare cause of congenital hypercoagulability. It is estimated to appear in 1% of young subjects with thrombosis of unknown origin.

Plasminogen congenital deficiency

Clinically similar to the antithrombin III and protein C deficits.

Sticky platelet syndrome

Gives rise to arterial and venous thrombosis.

Sickle-cell anemia (8% heterozygotic Afro-Americans and 1/600 of homozygotic Afro-Americans)

The main complications arise from vessel occlusion in arteries and veins, although mainly in the former. It can affect all types of vessels, with a preference for the smaller ones.
ACQUIRED DISORDERS

In addition to congenital coagulation alterations, other factors can enhance hypercoagulability:

1. Hepatic or endothelial damage, due to being the origin of coagulation factors.
2. Substrates deficit: vitamin C deficit.
3. Oral contraceptives, alcohol, tobacco.
4. Special situations such as old age, menopause, pregnancy, immobility, surgery, traumatisms.
5. Neoplasia, myeloproliferative diseases, disseminated intravascular coagulation (CID), sepsis, hyperviscosity syndromes.
6. Hyperhomocystinemia.
7. Antiphospholipid antibody syndrome.

Hyperhomocysteinemia

In this disorder, both genetic and acquired factors come into play. Homocystein is an amino acid derived from methionin which can become cystein. This conversion requires the presence of vitamins B12, B6 and folic acid. Subjects with mutations of the methylene-tetrahydrofolate-reductase enzyme (MTHFR), cystationase β-synthesase or with a deficit of essential vitamins for their metabolism can exhibit an excess of homocystein. This increase in blood has been associated to venous thrombosis and arterial disease (4).

Antiphospholipid antibodies

The prevalence of antiphospholipids antibodies in the general population include repetitive abortions, venous thrombosis and thrombocytopenia. Said antibodies constitute a heterogeneous family of antibodies with crossed sensitivity and can be detected by means of the ELISA technique. The lupic anticoagulant prolongs the cascades of phospholipid-dependent coagulation. The lupic anticoagulant test is more specific for patients at risk of thromboembolic events. On the contrary, the anticardiolypine antibodies test is more sensitive but less specific and may produce false positives. The isotype which is frequently involved in thrombosis is IgG, specifically IgG2 (1).

RECOMMENDED PANEL IN HYPERCOAGULABILITY STATES

It is very important to carry out a complete anamnesis to assess the existence of acquired risk factors because the confluence of a variety of congenital and acquired risk factors may have synergistic action.

There are several tests which must be carried out systematically when a hypercoagulation state is suspected (Table I) (1).

By way of guideline, the majority of congenital defects will increase the risk of venous but not arterial thrombosis.

In the Caucasian population with venous thrombosis, the markers involved are as follows (in order of frequency):

1. Leiden Factor V (12-40%).
2. Homocysteine (10-20%).
3. Mutation G20210A of prothrombin (6-18%).
4. Deficiencies of antithrombin III, Protein C and Protein S (5-15%).
5. Antiphospholipids antibodies syndrome (5-10%).

As regards arterial thrombosis, the markers most frequently involved are the homocystein levels in fasting and the antiphospholipids antibodies syndrome.

OPHTHALMOLOGICAL PATHOLOGIES AND HYPERCOAGULABILITY

There are specific neuro-ophthalmic or retinal pathologies in which the study can be more selective, as described below.

Venous obstructions of the retina

Retina venous occlusions (RVO) are differentiated from other types of venous thrombosis in their different pathogenesis and risk factors, the role of high intra-ocular pressure (IOP), the delicate structure of the retina, the absence of embolic complications and the inefficiency of fibrinolytic agents.

The most frequently involved factors in RVO high arterial pressure, diabetes, hyperlipidemia, glaucoma, tobacco and atherosclerosis. Lypoprotein A can be hypo-fibrinogenolytic because its amino acid
sequence is similar to plasminogen, leading it to compete with fibrin at the place of union and accordingly inhibiting its degradation. This could be a reason why hyperlipidemia is a risk factor for RVO (5).

Isolated and contradictory studies have attempted to establish a relationship of RVOs with the levels of protein C and S, antithrombin III, Leiden Factor V/resistance to APC, polymorphism of the gene G20210A of factor II (prothrombin). At this time there is not enough evidence to carry out a systematic study of these factors in patients with RVO (5-8).

In addition, high levels of FAP-1 have been found in patients with RVO compared to normal subjects. Patients with RVO exhibit a level of 4G polymorphism of gene FAP-1 which is significantly high [88% in patients with RVO compared to 63% in control patients (p = 0.03)], associate to hypo-fibrinolysis. Even though these results are of interest, for the time being there is not enough evidence to recommend the systematic study of FAP-1 in patients with RVO (5,9,10).

The role of antiphospholipids antibodies seems to be clearer, particularly in patients without known risk factors. In addition, the detection of antiphospholipid antibodies has important diagnostic and therapeutic implications because it facilitates the diagnostic of a possible self-immune disease or a primary antiphospholipid syndrome, with the ensuing indication of anticoagulation and close follow-up of the immunological situation (10.11).

Moderate increases of homocystein in the plasma of patients with OVCAR have also been described. Vitamin therapy would be effective to reduce these levels in this group of patients, but its actual efficiency for preventing new OVCAR events has not been established (7).

Due to the low prevalence of many of these rare diseases, many tests could give abnormal results and false positives. If the test is positive, the hematologist must confirm the condition prior to establishing a diagnostic or initiating treatment.

Final recommendations of hypercoagulability studies in RVO

– Anamnesis:
  • Discard family or personal thrombosis history.
  • Discard secondary causes for RVO (glaucoma with angular closure, severe dehydration, inflammatory retinal diseases, congenital tortuosity of retinal veins).

– Required Explorations:
  • Arterial pressure.
  • IOP.
  • Complete hemogram, hemoglobin and lipidic profile.

Hypercoagulability screening: Indicated in younger patients without known risk factors. These tests must not be performed routinely in patients with known risk factors. In elderly patients without known risk factors, we should consider only homocystein and antiphospholipid antibodies studies (it is unlikely that elderly patients without risk factors will debut with a primary thrombophylia) (5).

To summarize, the hypercoagulability screening tests (table II) in RVO shall be performed on (5):
  • Patients with bilateral and simultaneous RVO.
  • Patients under 50 without identifiable risk factors.
  • Thrombosis personal or familiar history.

Central retinal artery occlusion (CRAO)

Typically, this occlusion appears in elderly subjects around their sixties. It expresses unilaterally and with greater prevalence in men. On many occasions it is not possible to establish the exact pathogenic mechanism which leads to the occlusion of the central retinal artery. However, in most cases it responds to some of the following occurrences: embolism (most frequent) (12), intraluminal thrombosis, hemorrhage under atheroma plate, vasculitis, vessel spasm, nocturnal arterial hypopressure, desiccating aneurysm and high pressure arterial necrosis.

Due to the high prevalence of carotid atherosclerotic disease (45%) associated to CRAO, a supraauric trunks eco-Doppler is a routine indication for all patients (13). An echo-cardiographic study is necessary in subjects with a high cardio-emboligen risk (for instance, valvular prostheses), absence of carotid pathology, as well as in all patients under the age of 45 (14).

Even though coagulation disorders are typically related to venous occlusion disease, in young subjects under 45 and mainly in those under 30 the protein C and S deficit as well as the antithrombin III deficit (15,16) and hyperhomocistinemia (17) can cause acute arterial occlusion.

Some cases of CRAO have been described in patients with Leiden Factor V. However, due to the high frequency of this mutation in the general pop-
ulation, the association in these cases is considered to be fortuitous. Neither prothrombin mutation G20210A of prothrombin seems to play a relevant role in subjects over 45 years of age (18-20).

The presence of antiphospholipid antibodies has been related to chronic ischemic retinopathies in which CRAO or branch retinopathy is common. Even though the systematic search for these immunological markers is not well established, some studies point to a higher frequency thereof in young subjects under 50 with retinal vaso-occlusive conditions as well as in subjects without other risk factors (11,21,22).

Finally, sickle cell anemia can become complicated with retinal vasculopathy. Some studies point to an occlusion of the retinal central artery as the primary cause (23).

**Summary of hypercoagulability study in CRAO**

In patients under 45-50 with CRAO without justifiable cause a screening for pro-thrombotic diseases must be carried out including:

- Protein C, S and Antithrombin III.
- Homocistein.
- Hemoglobin electrophoresis (discard sickle cell disease in colored subjects).
- antiphospholipid syndrome (anti-cardiolypine antibody and lupic anticoagulant).

**Anterior ischemic optic neuropathy**

Anterior ischemic optic neuropathy (AION) represents a multi-factor ischemic event of the optic nerve. The factor which gives rise to the condition is usually not to a thromboembolic event but nocturnal arterial low pressure with transient reduction of the optic nerve perfusion pressure which reaches critical levels (24).

Even though the literature describes unusual AION cases in patients with coagulation disorders, at this time there aren’t enough arguments to request hypercoagulability studies in these patients.

**Temporary visual loss**

Some patients in a hypercoagulability state might exhibit temporary visual loss events, which
are normally secondary to a temporary occlusion of the central retina artery or its branches. It may course in association with any coagulation abnormality which causes arterial occlusion. The antiphospholipids antibodies syndrome and essential thrombocytosis are the most common causes (25). In over half of 50 patients with antiphospholipid antibodies in a retrospective study, temporary visual alterations were recorded including blurred vision, partial defects of the visual field and amaurosis fugax, in addition to permanent visual alterations (26).

Glueck et al (27) studied 19 patients with amaurosis fugax without detectable embolic source. They found thrombophyllic disorders such as increased Factor VIII and IX, heterozygote state for prothrombin G20210A, reduced levels of C and S proteins, MTHFR mutation and PL A1/A2. They also found hypo-fibrinolytic disorders such as increased lipoprotein A. According to the etiology, the patients were treated with cumarinics, aspirin, enoxaparin, vitamin B6 and B12 supplements, folic acid, etc., to achieve the disappearance of said visual symptoms.

**Hypercoagulability study in PVT**

In the presence of amaurosis fugax without carotid atherosclerosis or another embolic source, it is recommended to look for coagulation disorders and specifically alterations related to arterial occlusions, mainly the following:

- Antithrombin III.
- Homocysteine.
- Antiphospholipid syndrome.
- Hb electrophoresis (sickle cell disease in the black race).

The majority of said disorders are treatable.

**FINAL RECOMMENDATIONS**

- When hypercoagulability is suspected, a screening for congenital and acquired risk factors must be made.
- Usually, multiple risk factors must converge for developing thrombosis
- In the case of negative results and a high suspicion, an expert hematologist must be consulted, who will frequently recommend additional tests and provide long term treatment indications.

- In the presence of congenital factors it is recommendable to carry out a genetic assessment and counseling.
- The presence of acquired risk factors could increase the pre-existing risk of thrombosis; therefore, specific recommendations must be made on the issues such as contraception, hormonal substitution therapy, pregnancy, tobacco, etc.

**REFERENCES**


