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## Editorial

### Treatment of intraocular pressure independent phenomena in pseudoexfoliation syndrome<sup>☆</sup>

### Tratamiento de los fenómenos no dependientes de la presión intraocular en el síndrome de pseudoexfoliación

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The pseudoexfoliation syndrome is characterized by a systemic accumulation of a specific fibrillar substance with a complex composition of glucoproteins/proteoglycans as well as a high content of elastic microfibrillar components. Although its origin is not yet fully defined, two simple nucleotide polymorphisms have been isolated in the lysil-oxidase-like 1 gene region in chromosome 15 which could be involved in the development of the pseudoexfoliation syndrome.

Said gene is involved in the formation, stabilization and remodeling of elastic fibers. Hypotheses on its origin include an excessive secretion of said elastic microfibrils associated to oxidative stress increase that assume a characteristic arrangement through a cross-linking enzymatic process, with ensuing accumulation and interruption of the exit of aqueous humor through the trabecular mesh. To this aggregation we must add the finding of an increased concentration of free radicals and of 8-iso-prostaglandin F<sub>2</sub> in the aqueous humor of these patients, reinforcing the inflammatory action and the influence of oxidative stress in the pathogenesis of this syndrome.<sup>1</sup> These characteristics determine a particularly aggressive behavior that we consider to be the main cause of secondary open angle chronic glaucoma.

Accordingly, this syndrome generally presents with higher daytime intraocular pressure peaks, greater campimetric loss and optic nerve damages at diagnostic together with lower response to medical treatment and increased need of surgery for controlling it.

To give us an idea about the severity of this condition, the following question can be made: which other chronic open angle glaucomas are associated to peripupillary transillumination defects, pigmentary dispersion, guttata-like endothelial count reductions, zonular fibers rupture and even advanced cataract development?

At the systemic level, pseudoexfoliation material has been isolated in various organs including the heart, liver, kidneys, lungs and meninges. In extraocular locations, the pseudoexfoliation material is mainly found in the connective tissue of organs, frequently in the periphery of blood vessels, derived from connective tissue fibroblasts, smooth and striated muscles and cardiac muscular cells. These findings have led this syndrome to be considered as an elastosis, which would justify a possible association with abdominal aortic aneurysms.<sup>2</sup> Following said findings, the vascular pathology associated to the pseudoexfoliation syndrome is increasing. The syndrome has been related to ocular ischemia signs such as the presence of

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iridian neovessels, alteration in the flow and occlusion of the retina central vein, cardiovascular and cerebrovascular alterations and asymptomatic dysfunction of the myocardium and thick vessels.<sup>3,4</sup> In addition, the literature describes a possible association with other cardiovascular risk factors such as higher homocysteine levels, lower levels of vitamins B6, B12 and folates.<sup>4</sup>

Confirming the above hypotheses, a study carried out by our service demonstrated a greater prevalence of ischemic cardiopathy in patients with pseudoexfoliation, with said prevalence increasing together with higher pseudoexfoliation levels measured following a specially designed classification and according to signs that can be identified at the ophthalmological level.

The origin of this increased ischemic cardiopathy risk in patients with pseudoexfoliation syndrome is due to the endothelium dysfunction caused by the aggregation of pseudoexfoliation material in the adventitious and the subendothelial connective tissue of the vessel walls. The physiopathogenic mechanism of this endothelial dysfunction could be related with an increase of fibrosis and elastosis of the middle tunic as well as to an alteration of self-regulation mechanisms involving nitric oxide (ON) that increase oxidative stress.<sup>4,5</sup> This increase of oxidative stress seems to be related with diminished levels of B-type liposoluble vitamins (folic acid and vitamins B6 and B12), mainly in medication with vasodilating factors such as synthase nitric oxide, stable homocysteine levels and a clear antithrombotic and antioxidant character.

As a result of said alteration of metabolism and the appropriate endothelial function, homocysteine levels increase giving rise to higher oxidative stress and platelet aggregation.

On the other hand, diminished folic acid and pyridoxin levels seem to contribute to the trabecular mesh damages of these patients. Accordingly, low folic acid levels are related to an alteration of the cytoskeleton and extra-cellular matrix

cell signalling genes. Pyridoxin also plays a role in maintaining extracellular matrix integrity. In addition, lysil oxidase is inhibited by homocystein and therefore any increase in its levels could influence the production, deposit and degradation of trabecular mesh elastic fibers.<sup>1</sup>

We consider that hyperhomocysteine screening should be considered in patients with pseudoexfoliation, particularly in those with bilateral involvement and alterations in midriasis (according to the findings of our study), because high homocysteine levels constitute a known risk factor for the development of ischemic cardiopathy, which has been demonstrated to be more prevalent in patients with pseudoexfoliation.

Although additional studies are required to confirm the above hypothesis, treatment with nutritional supplements including folic acid, cyanocobalamine and pyridoxin constitute new therapeutic options to be considered in future clinical trials to assess their effectiveness in the prognosis and evolution of patients with pseudoexfoliation glaucoma.

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