What is a biological marker? According to the Spanish Language Royal Academy, it is any easily detectable atom or substance which allows for the identification of physical, chemical or biological processes. In biomedicine we refer to biological markers as the molecules we are able to determine in bodily tissues and fluids by means of lab techniques and which, according to their characteristics, function and availability, facilitate the diagnosis and prognosis of a specific condition, and as essential aid for identifying the most vulnerable subjects in a given population. If we take into account that there are about 600 neurological diseases and that only a few biomarkers are available for them, we will obviously support this field of research. Some biomarkers have been related to normal and pathological processes or as a pharmacological response to some therapies. In the literature we find markers linked to inflammations, ischemia-reperfusion, cancer and neurological degeneration processes, among others (1).

Glaucoma is one of the main causes of blindness the world over. The most frequent type of glaucoma is the primary open angle glaucoma (POAG) accounting for about 60% of cases. The onset is non-symptomatic and it is sometimes detected due to high intra-ocular pressure (IOP ) and in others due to loss of vision, the latter being the expression of irreversible damage (2). Accordingly, all studies focused on signs and symptoms pointing to the initial stages and the progression of this disease are crucial to prevent glaucoma patients from going blind. In recent years, strategies have been developed for identifying new molecules involved in this disease which, together with other well known diseases, may assist in establishing the etiopathogenic mechanisms of glaucoma. Firstly, we must consider that glaucoma comprises a group of different processes having the end result in the death of ganglionary retinal cells, expressed in the loss of optic nerve fibers which, in turn, has a functional expression in the loss of visual field and excavation of the optic nerve head. Glaucoma cases in which high IOP predominates are characterized by alteration of the trabecular mesh which causes a reduction in the exit of aqueous humor. Glaucoma is a mechanism which is independent of IOP and are associated to little known factors in the context of the disease including ischemia, inflammation, genetic predisposition, cardiovascular disease, self-immune processes, toxic habits, etc. High IOP damages the structures of the anterior chamber angle, causing the sedimentation of pigment and elastic fibers, calcifications and a variety of anomalies in the endothelial cells of the internal wall of Schlemm’s canal (3). In the course of the disease the neural tissue is selectively affected, with injury and death of retina ganglionary cells due to apoptosis and the loss of optic fibers.

If we take into account current knowledge on the issue, can it be said that we have reliable biomarkers for the glaucomatous disease? Unfortunately, to date there aren’t any molecules which can be specifically related to glaucoma, although current research is focusing on the search of markers to help us to: 1) differentiate between glaucoma types, 2) assess the progression of the disease, 3) identify the population most at risk, and 4) approach the design of specific therapies or, in other terms, the develop-
Oxidative stress.- At the etiopathogenic level, oxidative stress has been related to trabecular mesh anomalies and apoptosis of ganglionary cells in open-angle glaucoma. As early as 1996, Tamm et al (4) related these lesions with oxidative stress, concluding that the over expression of alpha B-crystalline protein in trabecular mesh cell cultures could be related to the intensity of the glaucomatous damage. Thereafter, Izzotti et al (5) demonstrated the existence of oxidative damage on the DNA of trabecular mesh cells in open-angle glaucoma patients, expressing by means of a significant increase of 8-hydroxyguanosine. Ferreira et al (6) studied the antioxidant enzymatic activity of dismutase superoxide and glutathione peroxidase as well as the total antioxidant capacity in the aqueous humor of glaucomatous patient, concluding that these can serve as markers because oxidative stress causes a global reduction of antioxidant activity. Along the same line, other studies have demonstrated in vitro the presence of metabolites of lipid peroxidation such as malondiadehyde (MDA) and 4-hydroxy-2-nonenal (4HNE) in relation to glaucomatous damages, observing the selective damage to ganglionary cells which can be counteracted by antioxidant enzymes (7). Our research group has demonstrated the presence of oxidative stress in the aqueous humor of patients scheduled for anti-glaucomatous surgery. Some of the issues yet to be elucidated include determining whether or not oxidative stress is the main cause of the glaucomatous disease or the consequence thereof.

Cell Survival and Death.- Several research groups, among them those led by E. Vecino, M.P. Villegas, M. Vidal, I. Vinuesa, J.M. Ramírez Sebastián and our own have studied the mechanisms of cell survival and death in glaucoma, with particular interest in apoptosis and neuroprotection. There is evidence to support the induction of apoptosis due to oxidative stress and that this process is detectable with relatively simple lab techniques, relating it to the progress of glaucomatous disease (8).

Within the complexity of the apoptotic cascade, the most relevant apoptosis biomarkers are the caspases (particularly caspase-3) and poly(ADP-ribose)polymerase (PARP-1). It has been demonstrated that PARP 1 can be utilized as an apoptosis marker in open-angle glaucoma, although there is a debate about the usefulness of caspase-3 (9). Other studies demonstrated the usefulness of protein bcl-2 as a cell survival marker as it inhibits death by apoptosis. In this regard, note must be made of the pigmented epithelium derived factor (PEDF) and the basic fibroblastic factor (bFGF) as additional important survival markers. Several studies describe their neuroprotective function against stimuli which induce apoptotic neuronal death in retina neurons and have been proposed as potentially useful in the development, maintenance and function of retinal cells. Continuing with this concept, neuroligal cells carry out essential functions for maintaining the neurons. Due to their relationship with blood vessels and optic axons, they participate directly in the electrolytic balance and metabolism of neurotransmitters (glutamate), they produce lamine, fibronectin and tropoelastin as well as a variety of growth factors (bFGF, TGF-b) or neuronal survival (NGF) (10).

Gene expression.- There are multiple risk factors for glaucoma such as age, race, severe myopia, diabetes, etc. Another risk factor is the family history of glaucoma. In fact, about 20% of glaucoma patients have family histories with the disease (11), which indicates that glaucoma exhibits an important genetic component. This is supported by the fact that the prevalence of open-angle glaucoma increases 1.8% in the general population and up to 13.5% among relatives of patients, as well as the fact that many ocular parameters are of hereditary nature such as IOP, resistance to ocular flow, papillary excavation and ocular dimensions (anterior chamber depth and axial length of the eye) (12). Numerous studies have been carried out following this line of research and it has been demonstrated that this disease is associated to several genes such as the myocillin gene, the optineurin gene or the CYP1B1 gene, which shows that the hereditary nature of primary open angle glaucoma is not in a single gene but in several. In addition, it may not be enough to have polymorphisms associated to glaucoma, it may be the interaction of the genes with the environment which produces the appearance of the disease.

In summary, many biomarkers have been studied in relation to primary open angle glaucoma but even so, and regardless of how much yet remains to be done to obtain clarity on the issue, it can be stated that the study and understanding of the genetic and
molecular bases of primary open angle glaucoma are essential for developing new therapies to halt the progress of glaucoma and prevent glaucomatous blindness.

REFERENCES

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