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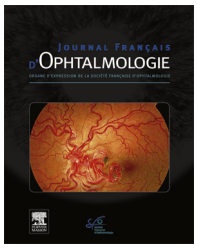

Formation médicale continue

RECOMMENDATIONS OF THE FRENCH SOCIETY OF OPHTHALMOLOGY

Management of Irvine-Gass syndrome☆

Prise en charge du syndrome d'Irvine-Gass

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Introduction

Irvine-Gass syndrome is a macular edema that develops following eye surgery. It was first described clinically in 1953 by Irvine [1] in his Proctor lecture, then characterized angiographically by Gass and Norton in 1966 [2]. Maumenee then referred it to as Irvine-Gass syndrome. It is the most common cause of postoperative decrease in visual acuity and represents a real therapeutic challenge. It may occur after surgery without complications but generally appears following intraoperative complications.

Epidemiology

Several studies have assessed the incidence of pseudophakic cystoid macular edema (CME) over the years, however, data is highly variable [3]. Indeed, this incidence depends mainly on the clinical definition, angiography, or optical coherence tomography (OCT) of Irvine-Gass Syndrome.

Clinically significant CME with decrease in visual acuity and metamorphopsia is only found in 1—2% [4] of patients with a peak incidence occurring on average 6 weeks post-surgery while subclinical CME, i.e. CME without visual impact, is found in about 30% [4] of patients on angiography and in 11—41% of patients on OCT despite preventive treatment [5,6]. Through improvements in phacoemulsification techniques, including a major decrease in incision size, incidence has significantly decreased and now ranges between 0.1 and 1.95% [7,8] with clinical impact. Incidence increases slightly in case of intraoperative complications. Identified risk factors include capsular rupture [9] and the use of iris retractors.

The presence of an epiretinal membrane, vein occlusion, uveitic or diabetic background [10], or the use of eye drops

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containing prostaglandins [4] increase the incidence of pseudophakic CME.

Pathophysiology

The pathophysiology of the Irvine-Gass syndrome is poorly understood but the cause is likely to be multifactorial. Several pathophysiological models have been proposed to explain the occurrence of postoperative CME; to date, an inflammatory origin seems more likely. Indeed, surgery results in a significant release of inflammatory mediators, including arachidonic acid, source of the inflammatory cascade, proinflammatory cytokines, lysozyme or VEGF. This leads to an impairment of the blood-retinal barrier and an increase in vascular permeability [11]. Then, fluids accumulate on the outer plexiform layer and inner nuclear layer forming cystic spaces that may form large fluid-containing cavities [12]. A mechanical origin has also been put forward to explain postoperative CME. Indeed, the vitreous traction force exerted on the macula during surgery may encourage the development of a CME [13]. The emergence of phacoemulsification has significantly reduced these traction forces in comparison to extracapsular extraction techniques which also explains the lower incidence of pseudophakic CME due to improvements in surgical techniques [14].

Diagnostic methods

As originally described by Gass, pseudophakic CME appears 4 to 12 weeks post-surgery [15], with a peak expected around week 6. Diagnosis is generally clinical. The patient describes a loss in vision, generally mild, of about 20/40, inconsistently associated with metamorphopsia. Examination of the anterior segment shows a white eye with minimal anterior chamber inflammation. Fundus examination reveals an isolated CME without hemorrhage, drusen or vascular anomaly. Some paraclinical examinations can help the diagnosis. The OCT shows cystoid spaces sometimes with a limited retrofoveal detachment of the photoreceptors. In some cases, mere thickening of the macula is identified [5]. At a time when OCT has become common practice, differentiating subclinical CME without functional impact from CME with functional impairment is critical to therapeutic decision-making [4]. In most cases, subclinical CME spontaneously regresses, at which point only close monitoring will be required. The early phases of fluorescein angiography [16] show macular leakage. The presence of a papillary leakage is common. This finding is useful in the differential diagnosis of the Irvine-Gass syndrome with diabetic CME that only very rarely shows papillary leakage. However, this examination is not necessarily required for the diagnosis. By contrast, when inflammatory signs such as hyalitis and/or vasculitis are present or when the disease is refractory, angiography becomes essential, in particular before treatment enhancement. Obviously, in case of uveitis, an etiological assessment is required prior to any treatment. In routine practice, pseudophakic CME is defined by a recent functional impairment reported by the patient and is associated with a macular edema visible on fundus examination, confirmed by OCT.

Therapeutic management

Preventive treatment

The use of anti-inflammatory eye drops, combining topical NSAIDs and corticosteroid eye drops, helps reduce the incidence of the Irvine-Gass syndrome by limiting postoperative inflammation [17]. Two topical NSAIDs have been granted a marketing authorization (MA) in the prevention of postoperative pseudophakic CME: flurbiprofen (Ocufen®) at a dosage of 1 drop into the conjunctival bag every 4 hours for 5 weeks, and nepafenac (Névanac®) at a dosage of 1 drop into the conjunctival bag of the operated eye, 3 times a day, starting on the day before cataract surgery then continued on the day of surgery and up to 60 days after surgery at the physician's discretion. An additional drop should be administered 30—120 minutes before surgery. Four other NSAIDs may be used as part of the MA for the prevention of inflammation usually triggered by surgery: ketorolac (Acular®) [18] at a recommended dosage of 1 to 2 drops 4 to 6 times a day for 21 days, starting 24 hours before surgery, and indomethacin (Indocollyre®) [19] 4 to 6 times a day to be started 24 hours before surgery. The latter appears to be as effective as ketorolac but is better tolerated [19]. Bromfenac (Yellox®) is recent and has the major advantage of only being instilled twice a day. The treatment starts the day after cataract surgery and only lasts 2 weeks. The last NSAID eye drops to be approved for this preventive indication in France is diclofenac (Dicloced®), at a dosage of 3 to 5 times a day for a maximum of 4 weeks, to be started 3 hours prior cataract surgery. Preventive treatment with topical NSAIDs for one month and topical corticosteroids for 15 days is usually used, but other protocols are available.

Curative treatment

To date, no randomized therapeutic study has been conducted to assess the course of action for the Irvine-Gass syndrome. Managing the Irvine-Gass syndrome is a true treatment escalation. A treatment combining the off-label use of oral acetazolamide (Diamox®) with topical NSAIDs is generally used as first-line therapy. Acetazolamide increases the retinal pigment epithelium pump function through the inhibition of carbonic anhydrase [20]. Usual dosage is highly variable depending on the authors, ranging from one-quarter tablet 4 times a day to 3 tablets of 250 mg of acetazolamide per day, most often with progressive decrease over a 1 to 3 month period. Acetazolamide is conventionally associated with NSAID eye drops for the whole duration of the treatment. Several publications have shown the efficiency of this association [21—23]. However, many adverse events are related to acetazolamide. The presence of an excessive fatigue, cramps or unpleasant tingling described by the patients, are source of non-compliance, resulting in an early recurrence of the CME upon treatment discontinuation. Regarding the use of topical NSAIDs as a curative treatment, a meta-analysis has shown that their use was beneficial for the treatment of chronic CME [17].

As a second-line therapy, various treatments may be used. We reiterate the importance at this stage to rule out a differential diagnosis, including uveitis, by performing