Société Française d'Ophtalmologie

MANAGEMENT OF IRVINE-GASS SYNDROME

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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 OCT (optical coherence tomography) 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 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[16]. 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[17] 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

1/ 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[18].

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®)[19] 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®)[20] 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[20]. 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.

2/ 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[21]. Usual dosage is highly variable depending on the authors, ranging from ¼ 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[22-24].

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[18].

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 at least a fluorescein and indocyanine green angiography before any treatment enhancement.

- Corticosteroids are frequently administered in the treatment of the Irvine-Gass syndrome. Indeed, corticosteroids block the release of arachidonic acid and, consequently, the inflammatory cascade. They also act on other inflammatory mediators such as interleukins or VEGF. They would also encourage fluid reabsorption by the retinal pigment epithelium.

  The efficiency of off-label subtenon injection of triamcinolone has been shown. Off-label intravitreal injections of triamcinolone have also shown their efficiency in the treatment of diabetic or uveitic macular edema and after ophthalmic surgery[26]. However, recurrences are common from 6 weeks to 3 months with variable efficiency of re-injections. In addition, the occurrence of serious complications such as hypertonia or pseudo-endophthalmitis makes it a limited indication.

  Invravitreal corticosteroid implants (Ozurdex®) are biodegradable implants delivering 700 micrograms of dexamethasone in the vitreous. Their efficiency has been demonstrated in a phase II study on uveitic macular edema conducted on 27 patients with Irvine-Gass syndrome. This study has shown an improvement of visual acuity in 54% of patients by over 15 letters after a 3-month follow-up[27].

  The European and US MA of Ozurdex® states that it is indicated for the treatment of adult patients with posterior segment inflammation such as non-infectious uveitis. However, the inflammatory pathophysiological mechanism of the Irvine-Gass syndrome could be assimilated to a posterior segment inflammation. Nevertheless, it should only be used as second-line therapy.

  The EPISODIC study[28] is a recent national, multicentric, retrospective series assessing the efficiency and safety of Ozurdex in 50 patients with pseudophakic CME resisting first-line therapy. A mean VA gain of 15.7 and 7.4 letters was obtained, respectively, after a 2- and 4-month follow-up. Less than 50% of patients experienced an anatomical and/or functional recurrence within 5.1 months with a similar efficiency profile after a second injection. In this study, less than 20% of patients experienced intraocular hypertonia (16% with IOP $\geq$25 mmHg) treated and controlled with eye drops alone. Based on these results, the use of Ozurdex appears interesting in this indication. In practice, it seems reasonable to wait three months before administering the first intravitreal injection, although some refractory and/or severe cases may benefit from an injection of Ozurdex after a 1 month of treatment. The same applies in the event of an intolerance or contraindication to acetazolamide with inefficiency of NSAID eye drops. Theoretically, the longer it takes to receive appropriate care, the less likely are the chances of functional recovery.

- Off-label anti-VEGF intravitreal injections may be used in the event of failure or contraindications to corticosteroid intravitreal injections. Their efficiency in

this indication, however, remains controversial. A series carried out on 16 eyes has shown no benefit in treating the refractory CMEs with first-line therapy[29], while another series conducted on 10 patients has shown a gain of 2 ETDRS lines with a decrease in macular thickness[30].

- Surgical treatment may be required in the event of capsule rupture with vitreous loss. Performing anterior vitrectomy associated with triamcinolone injection during cataract surgery with capsule rupture reduces the risk of CME[31]. Once the CME formed, posterior vitrectomy with internal limiting membrane peeling and reconstruction of the anterior segment may reduce or resolve the CME.

- When predisposing background or risk factors are present, it is essential to also treat the cause. The discontinuation of prostaglandin eye drops may help reduce the CME although this data is still controversial. Controlling diabetes and blood pressure is essential for diabetic patients. Similarly, controlling inflammation is necessary in patients with uveitis. In case of ischemic vein occlusion, treatment of the ischemia with pan-photocoagulation should be performed during the preoperative period in order to limit inflammation and, consequently, the Irvine-Gass syndrome.

Conclusion

The Irvine-Gass syndrome is a true therapeutic challenge. On the one hand, patients expect immediate visual recovery after cataract surgery and, on the other hand, the persistence of chronic macular edema is at risk of permanent sequelae.

Despite the spontaneous improvement of over 80% of cases of pseudophakic CME, therapeutic management is still very unclear.

While first-line therapy is effective in most patients, persistence of edema beyond the third month requires treatment adjustment.

It is important to reiterate, however, that so far most treatments are used off-label in this indication.

In practice, it is recommended to use a preventive peri-operative treatment combining NSAID eye drops, initiated a few days before surgery or on the day of surgery, and corticosteroid eye drops.

In case of obvious CME with visual loss, curative treatment should be considered. First-line therapy combines acetazolamide per os with a topical NSAID. In the event of failure of a well-managed treatment over a period of 1 to 3 months or an intolerance or contraindications, a therapeutic switch is recommended. The off-label subtenon or subconjunctival injection of triamcinolone is effective. The use of a dexamethasone implant in this indication appears to be an interesting new therapeutic option for refractory CMEs. It indeed often allows for an early and sustainable resolution, preventing the appearance of permanent macular alterations.

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