



**HAL**  
open science

## Sympathetic ophthalmia: long outcome

Beverly Casalan

► **To cite this version:**

| Beverly Casalan. Sympathetic ophthalmia: long outcome. Sensory Organs. 2020. dumas-03346753

**HAL Id: dumas-03346753**

**<https://dumas.ccsd.cnrs.fr/dumas-03346753>**

Submitted on 16 Sep 2021

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



**UNIVERSITÉ DES ANTILLES 2020**

**FACULTÉ DE MÉDECINE  
HYACINTHE BASTARAUD**

**N° 2020ANTI0537 /Thèse**

## **Ophtalmie sympathique : suivi au long-cours**

### **THÈSE**

Présentée et soutenue publiquement à la Faculté de Médecine Hyacinthe BASTARAUD des Antilles et de la Guyane et examinée par les Enseignants de ladite Faculté

**Le 16 octobre 2020**

En vue d'obtenir le grade de **DOCTEUR EN MEDECINE**

Par

**Beverly CASALAN**

Devant le jury composé de :

<b>Monsieur le Professeur Thierry DAVID</b>	Président, Juge
<b>Monsieur le Professeur Harold MERLE</b>	Juge
<b>Monsieur le Professeur Maturin TABUE TEGUO</b>	Juge
<b>Madame le Docteur Laurence BERAL</b>	Juge
<b>Madame le Docteur Christine FARDEAU</b>	Directrice de thèse



**Le Président de l'Université des Antilles : Eustase JANKY**

**Doyen de la Faculté de Médecine : Raymond CESAIRE**

**Vice-Doyen de la Faculté de Médecine : Suzy DUFLO**

<b>Professeurs des Universités - Praticiens Hospitaliers</b>	
<b>Pascal BLANCHET</b>	<b>Chirurgie Urologique</b> CHU de POINTE- À -PITRE/ABYMES Tel : 05 90 89 13 95
<b>André-Pierre UZEL</b>	<b>Chirurgie Orthopédique et Traumatologie</b> CHU de POINTE-A-PITRE/ABYMES Tel : 05 90 89 14 66
<b>Pierre COUPPIE</b>	<b>Dermatologie</b> CH de CAYENNE Tel : 05 94 39 53 39
<b>Thierry DAVID</b>	<b>Ophthalmologie</b> CHU de POINTE-A-PITRE/ABYMES Tel : 05 90 89 14 55
<b>Suzy DUFLO</b>	<b>ORL – Chirurgie Cervico-Faciale</b> CHU de POINTE-A-PITRE/ABYMES Tel : 05 90 93 46 16
<b>Eustase JANKY</b>	<b>Gynécologie-Obstétrique</b> CHU de POINTE-A-PITRE/ABYMES Tel 05 90 89 13 89
<b>François ROQUES</b>	<b>Chirurgie Thoracique et Cardiovasculaire</b> CHU de FORT- DE - FRANCE Tel : 05 96 55 22 71
<b>Jean ROUDIE</b>	<b>Chirurgie Digestive</b> CHU de FORT- DE - FRANCE Tel : 05 96 55 21 01 - Tel : 05 96 55 22 71
<b>Jean-Louis ROUVILLAIN</b>	<b>Chirurgie Orthopédique</b> CHU de FORT- DE - FRANCE Tel : 05 96 55 22 28
<b>André CABIE</b>	<b>Maladies Infectieuses</b> CHU de FORT- DE - FRANCE Tel : 05 96 55 23 01
<b>Philippe CABRE</b>	<b>Neurologie</b> CHU de FORT- DE - FRANCE Tel : 05 96 55 22 61
<b>Raymond CESAIRE</b>	<b>Bactériologie-Virologie-Hygiène option virologie</b> CHU de FORT- DE - FRANCE Tel : 05 96 55 24 11
<b>Maryvonne DUEYMES-BODENES</b>	<b>Immunologie</b> CHU de FORT- DE - FRANCE Tel : 05 96 55 24 24

<b>Professeurs des Universités - Praticiens Hospitaliers (suite)</b>	
<b>Annie LANNUZEL</b>	<b>Neurologie</b> CHU de POINTE- À -PITRE/ABYMES Tel : 05 90 89 14 13
<b>Louis JEHEL</b>	<b>Psychiatrie Adulte</b> CHU de FORT- DE - FRANCE Tel : 05 96 55 20 44
<b>Mathieu NACHER</b>	<b>Epidémiologie, Economie de la Santé et Prévention</b> CH de CAYENNE Tel : 05 94 93 50 24
<b>Magalie DEMAR - PIERRE</b>	<b>Parasitologie et Infectiologie</b> CH de CAYENNE Tel : 05 94 39 53 09
<b>Vincent MOLINIE</b>	<b>Anatomie Cytologie Pathologique</b> CHU de FORT DE FRANCE Tel : 05 96 55 20 85/55 23 50
<b>Philippe KADHEL</b>	<b>Gynécologie-Obstétrique</b> CHU de POINTE-A-PITRE/ABYMES Tel : 05 90 89 13 20
<b>Michel DEBANDT</b>	<b>Rhumatologie</b> CHU de FORT- DE - FRANCE Tel : 05 96 55 23 52
<b>Karim FARID</b>	<b>Médecine Nucléaire</b> CHU de FORT- DE - FRANCE Tel : 05 96 55 21 67
<b>Mehdi MEJDOUBI</b>	<b>Radiodiagnostic et imagerie Médicale</b> CHU de FORT- DE - FRANCE Tel : 05 96 55 21 84
<b>Rémi NEVIERE</b>	<b>Physiologie</b> CHU de FORT- DE - FRANCE Tel : 05 96 55 20 00
<b>Christian SAINTE-ROSE</b>	<b>Radiodiagnostic et imagerie Médicale</b> CHU de FORT- DE - FRANCE Tel : 05 96 55 20 00
<b>Sébastien BREUREC</b>	<b>Bactériologie &amp; Vénérologie</b> CHU de POINTE- À -PITRE/ABYMES Tel : 05 90 89 12 80
<b>Félix DJOSSOU</b>	<b>Maladies infectieuses et tropicales</b> CH de CAYENNE Tel : 05 94 39 50 50
<b>Nicolas VENISSAC</b>	<b>Chirurgie thoracique et cardiovasculaire</b> CHU de FORT- DE - FRANCE Tel : 05 96 55 20 00
<b>Moustapha DRAMÉ</b>	<b>Épidémiologie, Économie de la Santé</b> CHU de FORT- DE - FRANCE Tel : 05 96 55 20 00
<b>Christophe DELIGNY</b>	<b>Médecine Interne</b> CHU de FORT- DE - FRANCE Tel : 05 96 55 22 55

<b>Professeurs des Universités - Praticiens Hospitaliers (suite)</b>	
<b>Narcisse ELENGA</b>	<b>Pédiatrie</b> CH de CAYENNE Tel : 05 94 39 77 37
<b>Nadège CORDEL</b>	<b>Dermatologie &amp; Vénérologie</b> CHU de POINTE- À -PITRE/ABYMES Tel : 05 90 89 10 10
<b>Harold MERLE</b>	<b>Ophtalmologie</b> CHU de FORT- DE - FRANCE Tel : 05 96 55 20 00
<b>Pierre-Marie ROGER</b>	<b>Maladies infectieuses et tropicales</b> CHU de POINTE- À -PITRE/ABYMES Tel : 05 90 89 10 10
<b>Maturin TABUE TEGUO</b>	<b>Médecine interne : Gériatrie et Biologie du vieillissement</b> CHU de POINTE- À -PITRE/ABYMES Tel : 05 90 89 10 10
<b>CORDEL-WATTIER Nadège</b>	<b>Dermato-vénérologie</b> CHU de POINTE- À -PITRE/ABYMES Tel : 05 90 89 10 10

<b>Professeur de Médecine Générale</b>	
<b>Jeannie HELENE-PELAGE</b>	<b>Médecine Générale</b> CHU de Pointe-à-Pitre / Cabinet libéral Tel : 05 90 84 44 40

<b>Professeur Associé de Médecine Générale</b>	
<b>Franciane GANE-TROPLENT</b>	<b>Médecine générale</b> Cabinet libéral les Abymes Tel : 05 90 20 39 37

<b>Maître de Conférences des Universités - Praticiens Hospitaliers</b>	
<b>Jocelyn INAMO</b>	<b>Cardiologie</b> CHU de FORT- DE - FRANCE Tel : 05 96 55 23 72 - Fax : 05 96 75 84 38
<b>Fritz-Line VELAYOUDOM épouse CEPHISE</b>	<b>Endocrinologie</b> CHU de POINTE- À -PITRE/ABYMES Tel : 05 90 89 13 03
<b>Marie-Laure LALANNE-MISTRIH</b>	<b>Nutrition</b> CHU de POINTE- À -PITRE/ABYMES Tel : 05 90 89 13 00
<b>Moana GELU-SIMEON</b>	<b>Gastroentérologie hépatologie</b> CHU de POINTE-A-PITRE/ABYMES Tel : 05 90 89 10 10
<b>Véronique BACCINI</b>	<b>Hématologie</b> CHU de POINTE-A-PITRE/ABYMES Tel : 05 90 89 10 10
<b>Laurent BRUREAU</b>	<b>Urologie</b> CHU de POINTE-A-PITRE/ABYMES

	Tel : 05 90 89 10 10
<b>Maître de Conférences des Universités - Praticiens Hospitaliers</b>	
<i>(Suite)</i>	
<b>Clarisse JOACHIM-CONTARET</b>	<b>Épidémiologie, économie de la santé et prévention</b> CHU de FORT- DE - FRANCE Tel : 05 96 55 20 00

<b>Maître de Conférence des Université de Médecine Générale</b>	
<b>Philippe CARRERE</b>	<b>Médecine générale</b>

<b><u>Maître de Conférence Associé de Médecine Générale</u></b>	
<b>Franck MASSE</b>	<b>Médecine générale</b>
<b>KANGAMBEGA-CHATEAU-DEGAT Walé</b>	<b>Médecine générale</b>

## REMERCIEMENTS

Au Professeur Thiery David, merci de me faire l'honneur de présider ce jury. Je vous remercie chaleureusement pour votre disponibilité tout au long de ces années. Vos connaissances et votre savoir-faire autant en chirurgie qu'en médecine m'ont émerveillée et ont suscité chez moi une grande admiration et une recherche perpétuelle de perfectionnement.

Au Professeur Harold Merle, merci de me faire l'honneur de juger mon travail. Mes collègues ne tarissent pas d'éloges à votre égard, et j'ai un certain regret de ne pas être passée dans votre service.

Au Professeur Maturin Tabue Teguo, merci d'avoir accepté de faire partie de ce jury.

Au Docteur Laurence Beral, merci de m'avoir appris la rigueur et de m'avoir donné la volonté de toujours chercher à faire mieux. Le temps a passé depuis mon premier semestre comme Dona. J'espère être à la hauteur de ton investissement et de tes attentes aujourd'hui. Merci d'avoir été ma chef et mon amie.

Au Docteur Christine Fardeau, ma directrice de thèse. Merci pour votre implication sans limite. Vous êtes impressionnante par votre savoir et pour votre amour pour la médecine et en vos patients. Peu de médecins sont à votre niveau. Vous êtes incroyable. Ce fut un réel plaisir de travailler à vos côtés à la Pitié Salpêtrière et sur cet article. Je ne vous remercierai jamais assez.

Au Docteur Martin Bonnafous, merci d'avoir été si pédagogue en consultation avec moi. Tes consultations étaient un vrai moment d'apprentissage que ce soit en rétine ou en contactologie. Merci pour ta bonne humeur.

Au Docteur Daena Hobeika, merci de m'avoir appris que l'ophtalmo pédiatrique ce n'est pas l'enfer comme je le pensais au début. Ta patience et ton calme sont exemplaires.

Au Docteur Pierre Sustronck, tu m'as appris énormément de choses que ce soit en Guadeloupe ou à Créteil. Tu as été un super binôme. Mési an pil.

Au Docteur Sadri Chahed, vous m'avez transmis votre passion pour la chirurgie et je vous en suis reconnaissante. Merci de m'avoir donné les outils pour devenir une bonne chirurgienne.



Au Professeur Baram Bodaghi, pour m'avoir accepté dans votre service. Ce semestre d'inflammation fut passionnant.

Au Professeur Eric Souied, d'avoir suscité en moi cette passion pour la rétine médicale. Merci à vous et à votre brillante équipe de m'avoir appris que la réflexion ne s'arrête pas à : on injecte, on n'injecte pas. Merci de me donner l'opportunité de rejoindre votre service et de pouvoir en apprendre davantage.

Merci aux docteurs Francesca Amoroso, Olivia Zambrowski et au reste de l'équipe de Créteil. Travailler avec vous était exceptionnel.

A monsieur Mondésir pour vos fraises Tagada. J'ai hâte de vous entendre dire « Beverly dans mon bureau » en novembre. Vous avez toujours été disponible et à mon écoute.

Au Professeur Michel Paques et son équipe, le Docteur Julien Boumendil, le Docteur Julia Meney qui m'ont appris comme personne la chirurgie orbito-palpébrale, le Professeur Isabelle Audo avec qui j'ai passé des heures sur des cas de dystrophies rétinienne passionnantes, le Docteur Sarah Mrejen qui m'a ébloui par son savoir, sa gentillesse et son humilité. A Sandrine Dargent pour ton franc-parler et ta bonne humeur. Et merci au reste de l'équipe des XV-XX.

A Milka, pour notre amitié indéfectible depuis le collège. Merci d'être là pour me temporer et me remettre sur le droit chemin. Cette année est la tienne, je te souhaite le meilleur et encore félicitation. J'espère que nos projets se concrétiseront, je te veux dans ma vie, au quotidien. Comme dirait Princess Lover, tu es mon soleil dans ce service.

A Sophie qui est là dans les bons et les mauvais moments. Persévère, tu seras une super rétinologue chir.

A Arnaud, Selim, Nico, vous m'avez bien fait rire durant toutes ces années.

A Alex, Remi, Maxence et Martin. Je vous bouscule peut-être un peu mais c'est pour vous rendre meilleurs. Vous avez un potentiel incroyable, je crois en vous.

A Malik, Coralie et Gigi. Merci de votre aide à tout instant. A Isa, la meilleure des secrétaires. Vous me manquerez.

A Naiké, continue de nous éblouir avec ta joie de vivre et ta bonne humeur.

A ma team Forever Together: Arielle, Roxane, Meryem, Mika, Marvin, Alexis, Badr. Ayoub. Je pourrai en écrire des lignes sur vous. Plus que des co-internes, on est devenu des amis, des vrais. Grace à vous j'ai retrouvé la chaleur d'une famille loin de ma Guadeloupe.

A mon meilleur ami Ludo, tu as toujours été là pour moi. Même à 6h du mat quand j'ai besoin d'un jerrican d'essence. Notre amitié était improbable, et ça ne la rend que plus belle. Tu es un mec bien, vraiment.

A Marine, tu es exceptionnelle. Je t'aime fort.

A Cocobino, my brother from another mother. Tu m'as soutenu pendant mes plus dures années en médecine et je t'en remercie. Anguilla est notre madeleine de Proust. J'espère que nos enfants auront la même jeunesse que nous.

A Clémence et Stanley, votre amitié m'est chère.

A ma famille :

A mes parents, je n'aurais pas pu espérer mieux, vous êtes parfaits. Vous m'avez appris tant de choses. Merci pour votre amour et votre soutien indéfectible pendant toutes ces années. Je n'ai pas toujours été facile je le reconnais et je m'en excuse. Vous avez toujours cru en moi et j'espère que vous êtes fiers de moi aujourd'hui. Je vous dois ma réussite. Je vous aime de tout mon cœur.

A Céline et Gabriel, on est tous les 3 si différents mais en même temps si complémentaires. Vous m'inspirez chaque jour.

A Laurence, ma personne, tu me nourris, tu essuies mes larmes, tu rires avec moi. Tu as toujours été là et je ne veux pas que ça change. Et à Guillaume.

A François, Barbara, Caro, Kate, Melissa, j'ai eu la plus belle jeunesse possible grâce à vous.

A ma marraine.

A mes deuxièmes parents les Ramzay.

A Maurice, tu nous as quitté bien trop tôt.

A mes cousins, taties et tontons.

A Antony, tu me tires vers le haut et me pousses à me dépasser chaque fois. Merci d'être là. Je n'oublierai jamais ce jour où je t'ai vu et où j'ai su. Meredith a trouvé son Dr Shepherd comme diraient certains. Chetaume.

## **TABLE DES MATIERES**

<b>TITRE.....</b>	<b>p.12</b>
<b>RESUME.....</b>	<b>p.13</b>
<b>ABSTRACT.....</b>	<b>p.14</b>
<b>INTRODUCTION.....</b>	<b>p.15</b>
<b>MATERIEL AND METHOD.....</b>	<b>p.16</b>
<b>RESULTS.....</b>	<b>p.17</b>
<b>DISCUSSION.....</b>	<b>p. 21</b>
<b>BIBLIOGRAPHY.....</b>	<b>p.27</b>
<b>SERMENT D'HIPPOCRATE.....</b>	<b>p.33</b>



## **Sympathetic ophthalmia: long-term outcome**

Beverly Casalan<sup>1</sup>, Linda Hrarat<sup>1</sup>, Anthony Amaral<sup>1</sup>, Laurence Beral<sup>2</sup>, Christine Fardeau<sup>1</sup>

- 1) Department of Ophthalmology, Pitié-Salpêtrière Hospital, Reference center for rare diseases OPHTARA, Sorbonne Paris University, 47-83, boulevard de l'Hôpital, 75013 Paris, France.
- 2) Département of Ophthalmology, CHU de Pointe-à-Pitre/Abymes, route de Chauvel, Pointe-à-Pitre, Guadeloupe, France

Corresponding author: Christine Fardeau [christine.fardeau@aphp.fr](mailto:christine.fardeau@aphp.fr)

Department of Ophthalmology, Pitié-Salpêtrière Hospital, Reference center for rare diseases OPHTARA, Sorbonne Paris University, 47-83, boulevard de l'Hôpital, 75013 Paris, France.

Conflict of interest: none

Statut de l'article : en cours de soumission pour la revue « Eye »

## **RESUME**

**But** : Évaluer sur le long terme l'épargne cortisonique liée aux étapes successives de la prise en charge médico-chirurgicale de l'ophtalmie sympathique (OS)

**Méthodes** : les dossiers médicaux de patients avec OS suivi au moins 3 ans dans un centre de référence de maladies rares ont été analysés. On a étudié le facteur déclenchant, les symptômes et signes cliniques d'OS, le traitement et l'acuité visuelle.

**Résultats** : 10 patients correspondaient aux critères d'inclusion. Le délai médian d'apparition de l'OS était de 1,5 ans. A l'admission, la médiane de la meilleure acuité visuelle corrigée et de la dose journalière de cortico-dépendance était respectivement de 0,45 LogMar [0,2;0,65] et 40 mg [30;65]. Nous avons retrouvé un œdème maculaire inflammatoire chez 7 patients. La durée médiane de suivi des patients était de 14 ans [6,5;25]. A la fin du suivi, il n'y avait pas d'amélioration significative de la meilleure acuité visuelle corrigée  $p=0,87$  mais une diminution significative de la dose médiane journalière de corticostéroïdes à 8 mg [3,5;12,5]  $p<0,01$ . Durant le suivi des patients, le contrôle de l'inflammation et des œdèmes maculaires a été possible grâce à l'utilisation d'anti métabolites chez 4/6 patients, d'anti TNF-alpha chez 0/3 patients, de cyclophosphamide chez 0/1 patient, de cyclosporine chez 0/1 patient, d'interféron- $\alpha$ -2a chez 6/6 patients, d'immunoglobulines polyvalentes chez 0/1 patient, d'énucléation chez 0/3 patients.

**Conclusion** : L'Interféron- $\alpha$ -2a et les anti métabolites semblent utiles en cas d'œdème maculaire et pour l'épargne cortisonique contrairement à l'énucléation qui apparait péjorative dans l'évolution de l'uvéite dans cette petite série de patients.

## **ABSTRACT**

**Objective:** to evaluate retrospectively the long-term visual outcome and steroid-sparing related to successive steps of the medico-surgical management of sympathetic ophthalmia (SO).

**Methods:** medical records of patients with SO, followed in a reference center for rare diseases, for at least 3 years, were reviewed for history of ocular trauma or surgery and subsequent development of SO, presenting symptoms, treatments, and visual outcomes.

**Results:** Ten patients fitted the inclusion criteria. The median time of SO occurrence was 1,5 years. At admission, median best-corrected visual acuity (BCVA) was 0,45 LogMAR [0,2;0,65], median steroid dependence daily dose was 40 mg [30;65], and inflammatory macular edema was present in 7/10 eyes. The median time of follow up was 14 years [6,5;25].

At the end of follow-up, there were no significant improvement for the BCVA with a median of 0,4 LogMAR [0,1;0,75]  $p=0,87$ . However, the median daily prednisone dose was significantly decreased to 8 mg [3,5;12,5]  $p<0,01$ . At six months on prednisone associated to immunosuppressive drugs, inflammation and macular edema control was assessed using antimetabolites in 4/6 treatments, anti TNF-alpha in 0/3 treatments, cyclophosphamide in 0/1 treatment, cyclosporine in 0/1 treatment, interferon- $\alpha$ -2a in 6/6 treatments, polyvalent immunoglobulin in 0/1 treatment, enucleation in 0/3 treatments.

**Conclusion:** Interferon- $\alpha$ -2a and antimetabolites seemed to be useful in case of macular edema and in steroid sparing unlike enucleation which appeared to be pejorative in uveitis course in that small series.

**KEYS WORDS:** sympathetic ophthalmia, uveitis, immunosuppressive therapy, macular edema, retinal vasculitis, interferon

## INTRODUCTION

Sympathetic ophthalmia (SO) is a rare bilateral pan-uveitis following scleral infraction either after an accidental penetrating injury or due to multiple retinal surgeries to one eye.

The true incidence of SO remains difficult to establish and the literature reports are variable, likely owing to the fact that there is no ancillary test. Hence the diagnosis is based on medical history and clinical finding. A large immune and infectious check-up is needed to eliminate a differential diagnosis such as tuberculosis.

In 1982, Gass [Erreur ! Source du renvoi introuvable.] reported the prevalence of SO at 0.01% following pars plana vitrectomy, and a 0.06% after other penetrating ocular trauma. SO accounted for approximately 0.3% of the uveitis and the one-year incidence was calculated to be a minimum of 0.03/100,000 population [Erreur ! Source du renvoi introuvable.].

William McKenzie [Erreur ! Source du renvoi introuvable.] provided the first full clinical description of the disease in 1840. The histopathology was reported in 1905 by Ernst Fuchs as an infiltration of the uveal tract, particularly the choroid, and formation of nodular aggregations beneath the retinal pigment epithelium [Erreur ! Source du renvoi introuvable.]. Fuchs and Dalen independently described the inflammatory nodular aggregates as "Dalen-Fuchs nodules" [Erreur ! Source du renvoi introuvable.]. However, much is still to be elucidated about the pathophysiology [Erreur ! Source du renvoi introuvable.]. The etiology of SO has included two hypotheses: autoimmunity and/or trigger by an infectious agent during antigen exposure. In recent years, studies have emphasized the immune system producing ocular inflammation. That the injured eye, known as the exciting eye, and the contralateral eye, or sympathizing eye, demonstrate similar pathology suggests involvement of an autoimmune response. Rao and al [Erreur ! Source du renvoi introuvable.] suggest that infraction of the sclera participates in the development of SO by exposing uveo-retinal antigens in the conjunctival lymphatics and thereby induces a subsequent immunopathological response. Different retinal antigens have been suspected, including retinal soluble antigen, rhodopsin, interphotoreceptor retinoid-binding protein, recoverin and melanin antigen [Erreur ! Source du renvoi introuvable.], but the specific antigen responsible for SO is yet to be found.

The visual prognosis for established SO was originally very poor, with only approximately 50% of cases retaining useful vision [Erreur ! Source du renvoi introuvable.]. The use of



systemic corticosteroids (CS) and, more recently, immunosuppressive (IS) drugs has transformed the outlook of this potentially blinding disorder.

The rarity of the disease makes it difficult to establish any general consensus.

The purpose of this study is to evaluate retrospectively the long-term visual outcome and steroid-sparing related to successive steps of the medico-surgical management of SO.

## **METHODS AND PATIENTS**

This retrospective study, carried out in the ophthalmology department of La Pitié-Salpêtrière hospital, constitutive reference center for rare diseases, reports serial SO seen at the consultation between January 2006 and April 2020.

Inclusion criteria were a bilateral granulomatous pan-uveitis with a context of penetrating injury or intra-ocular surgery, with a negative check-up for infectious or auto-immune diseases and a follow-up for at least 3 years with IS therapy.

The clinical exam included best corrected visual acuity (BCVA) on decimal scale, converted to LogMar, biomicroscopy, tonometry, fundoscopy and analysis of the vitreous.

The degree of intraocular inflammation was evaluated according to the Standardization of Uveitis Nomenclature (SUN) Working Group [Erreur ! Source du renvoi introuvable.]. The Nussenblatt scale [Erreur ! Source du renvoi introuvable.] was used to evaluate the degree of vitritis. Active anterior segment inflammation corresponded to cell grade 0.5+ or higher or vitreous haze > 1+. Controlled uveitis corresponded to findings of < 0.5+ cell or descriptive terms such as “quiet, quiescent, and no active inflammation”.

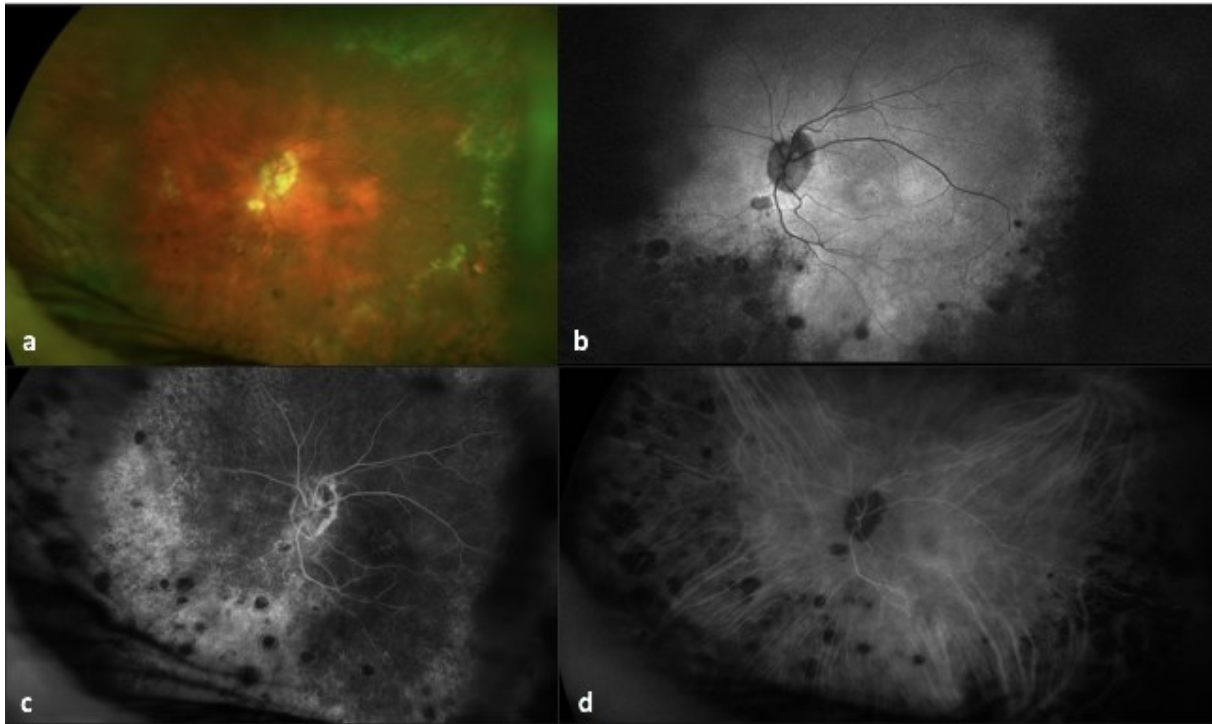
The central foveal thickness (CFT) was obtained automatically by a Spectral Domain OCT (Spectralis® HRA-OCT device, Heidelberg, Germany) for objective measurements and made by an optometrist that ignored the treatment regimen.

Fundus photographs were performed using Optos® California, autofluorescence and angiography using a Spectralis® HRA-OCT device (Heidelberg, Germany) and an Optos® California (**figure 1**), and automated flare measurement using a Laser Flare Meter (FC-1000 Kowa, Kowa Company, Japan).

Etiological testing was performed at the screening visit and included blood count, serum ionogram, sedimentation rate, protein electrophoresis, HIV, syphilis, Lyme serology, anti-DNA antibodies, IFN- $\gamma$  release assay QuantiFERON®, chest scan, tuberculin skin test and brain magnetic resonance imaging. Depending on the clinical findings, the etiological testing was extended with an aqueous humor sampling for herpes virus PCR, bacterial analysis, interleukin 10/6 measurement and other specific tests if necessary.

The primary endpoint was the steroid-sparing, between the admission time for uveitis activity and at the end of follow-up. The secondary endpoints were the BCVA, the anterior chamber

cells and the vitreous haze, the anterior flare and the central foveal thickness of the sympathetic eye.



**Figure 1** - a) Fundus photograph and corresponding b) autofluorescence c) fluorescein angiography and d) green indocyanine angiography illustrating chronic choroidal infiltrates (Dallen-Fuchs nodules) in sympathizing eye of patient with sympathetic ophthalmia.

Statistical analysis was performed using BiostaTGV. Population demographics and categorical variables were reported in median with interquartile (IQ). Wilcoxon Signed Rank test were used to compare the values at inclusion and at the end of follow-up. Results were considered statistically significant when  $p < 0.05$ .

## **RESULTS**

Thirteen charts were initially reviewed: 1 had short follow up, 2 had differential diagnoses including one case of orbital Malt lymphoma while the contralateral eye was traumatized 34 years earlier and one case of ocular tuberculosis proved histologically. Ten patients with a

diagnosis of SO fitted the inclusion criteria. Table 1 summarizes demographic details and clinical profile of the patients. Age at diagnosis ranged from 7 to 80 years, with a follow-up from 5 years to 29 years. Accidental penetrating injuries concerned youngest patients with a median of 12 years [7;15] than retinal detachment with a median of 51 years [35.5;73.5]  $p=0.02$ . The interval between injury or initial surgery and diagnosis ranged from 1 month to 34 years with a median of 1.5 years [0.26;5.5], with 5 cases developing SO within 1 year of insult (**Table 1**).

**Table 1** - Demographic details, clinical profile of 10 patients with sympathetic ophthalmia (SO)

Characteristics		
Age [median (IQR)] in yrs		51 (24-74)
Gender [No. (%)]	men	6 (60)
	women	4 (40)
Time to first presentation [median (IQR)] in yrs		1.5 (0.26-5.5)
Cause of inciting events [No. (%)]	trauma	3 (37,5)
	Post-surgery	6 (50)
	Choroidal melanoma	1 (12.5)
enucleation	yes	3
	no	7
Time between uveitis start and enucleation [median (IQR)] in yrs		1 (1-3)

Yrs – years; IQR – 25-75% interquartile range

At admission, all patients received topical dexamethasone, systemic prednisone with a daily median dose of 40mg [30-65]. One patient already had an IS therapy (Cyclosporine) and one patient had polyvalent immunoglobulin. Three patients underwent enucleation of the exciting eye 6 months prior to their first visit to our center, where 2 of three patients were referred for an uncontrolled inflammatory rebound of their sympathetic eye. All ten patients were referred to our center for steroid-dependence > 20mg/d. After admission, we started IS therapy for all patients.

At the end of follow up, 4 of 10 patients saw 0.3 LogMAR or greater; two saw 1.0 LogMAR or less. There was no significant improvement for the BCVA, with a median of 0.4 LogMAR [0.1;0.75] p=0.87. We found a significant steroid-sparing with a median dose of 8 mg [3.5;12.5] p<0.01. **Table 2** illustrates the steroid-sparing, visual and inflammatory outcomes of this small series.

**Table 2** – Steroid-sparing, visual outcome and inflammation outcomes of 10 patients with sympathetic ophthalmia.

	At inclusion	At the end of follow-up	p-Value*
Steroid use [median (IQR)] in mg	40 (30;65)	8 (3.5;12.5)	<0.01
BCVA – Log MAR [median (IQR)]	0.4(0.2;0.65)	0.4 (0.1;0.75)	0.5
Vitritis > 1+ [No. (%)]	4 (40)	0	
Flare anterior chamber [median (IQR)] in cells/0.5 mm <sup>3</sup>	35.8 (18.5;81)	21.2 (15.2;30.3)	0.06
Central Foveal Thickness [median (IQR)] in µm	332 (253;556)	259 (254;309)	0.04
Active Dalen-Fuchs nodule on angiography	4	0	

\*Wilcoxon signed rank test; IQR – 25-75% interquartile range

Throughout the history and follow-up, inflammatory control was assessed using antimetabolites in 4/6 treatments, ADA in 0/3 treatments, cyclophosphamide in 0/1 treatment, cyclosporine in 0/1 treatment, IFN- $\alpha$  in 6/6 treatments, enucleation in 0/3 treatments. Slow withdrawal of treatment was attempted once inflammatory control was established. The median time of follow up was 14 years [6,5;25]. At the end of follow-up, 8/10 patients were still receiving systemic CS. For the two other patients we were able to stop CS with IFN- $\alpha$  et AZA. 3 patients stopped IS therapy and were treated only with CS; one due to side effect (digestive disturbance) with MMF, one because the patient did not want to continue the treatment due to asthenia with IFN and one because of a good inflammatory control with 7mg of CS. **Table 3** summarizes the various types of IS therapy used in the management of

SO with the steroid-dependence threshold for each patient. Steroid dependence by IS are listed in **Table 4**.

**Table 3**– Treatment of ten patient with sympathetic ophthalmia for more than 3 years

Patients	Age at diagnosis (years)	Cause	Immunosuppressive therapy strategy (Steroid dependence in mg)	Systemic steroid (mg)	
				At inclusion	At the end of follow-up
1	80	RD	AZA (0)	70	0
2	55	RD	ADA (20) ; MMF (7)‡	60	15
3	46	PI	IFN (8)	50	8
4	79	Choroidal melanoma	CP (30); IFN (10)	70	10
5	7	PI	Cyclosporine (30); AZA (7)	35	7
6	15	PI	Ig (25) ; AZA (20) ; IFN (10) ‡	11	15
7	57	RD	AZA (25) ; ADA (20) ; IFN (10)	40	10
8	32	RD	IFN (0)	30	0
9	69	RD	ADA (20); IFN (7) ‡	40	7
10	47	RD	AZA (8)	25	8

RD: Retinal detachment; PI: penetrating injury; AZA: Azathioprine; ADA: Adalimumab; MMF: Mycophenolate mofetil; CP: cyclophosphamide; IFN: interferon alpha2a; Ig: polyvalent immunoglobulin ‡ discontinuation of immunosuppressive therapy

**Table 4** – Steroid dependence for each treatment for 10 patients with Sympathetic ophthalmia

Treatments	Number of patients	Steroid dependence [median (IQR)] in mg
Antimetabolites	6	8 (3,5;22,5)
Interferon- $\alpha$ 2a	6	9 (3,5;10)
Cyclophosphamide	1	30
Cyclosporine	1	30
Polyvalent immunoglobulin	1	25
Adalimumab	3	20 (20;20)

Relapses occurred in 2 patients during follow-up and required increase in CS therapy. One because the patient stopped all of his treatment including oral prednisone and IFN- $\alpha$ . And the second while being treated with ADA.

Type 2 choroidal neovascularization occurred in 3 patients, promptly successfully treated with ranibizumab intravitreal injection and transient high daily doses of prednisone, increased at 1mg/kg/d for 7 days and slowly tapered. This complication occurred while the treatment included IFN- $\alpha$  once a week and 5 mg/d of CS for 1 patient, ADA for the second patient and only CS for the third patient.

At the end of follow-up, the side effects were a gain weight >5kg for 4 patients, two corticoid induced diabetes, lymphopenia at 750/mm<sup>3</sup> for one patient treated by IFN- $\alpha$  requiring a lower dose, one mood disorder requiring a lower dose of IFN- $\alpha$  (once a week), one digestive disturbance under mycophenolate-mofetil (MMF). None raised intraocular pressure.

## **DISCUSSION**

In our retrospective monocentric study, we present the different clinical characteristics and long-term management of ten patients with SO.

In our retrospective study, we based our diagnosis on chart review. The difficulty with SO is that it remains a clinical diagnosis with numerous differential diagnoses like idiopathic bilateral uveitis. It is considered as a diagnosis of exclusion. We based our diagnosis on a body of arguments such as the medical history, a large infectious, tumor and autoimmune negative screening, the absent of history of a uveitis prior to the penetrating injury or intraocular surgery according to the literature [Erreur ! Source du renvoi introuvable.][Erreur ! Source du renvoi introuvable.].

Penetrating trauma used to be described as the most common cause of SO [Erreur ! Source du renvoi introuvable.][Erreur ! Source du renvoi introuvable.][Erreur ! Source du renvoi introuvable.][Erreur ! Source du renvoi introuvable.]. Our findings are consistent with more recent studies which report that the most common cause of SO is after surgery [Erreur ! Source du renvoi introuvable.][Erreur ! Source du renvoi introuvable.][Erreur ! Source du renvoi introuvable.]. The authors attributed this decline in trauma-induced SO to the strict industrial safety laws that mandate the use of appropriate personal protective equipment at work. With the advancements in vitreoretinal surgical

instruments and training, ophthalmologists are operating on more cases, including complex cases and multiple surgeries or procedures, which would have been given up in the past [Erreur ! Source du renvoi introuvable.]. SO is usually described as more common in men. This gender predilection has been attributed to the increased exposure to trauma in men [Erreur ! Source du renvoi introuvable.]. In our study we found more men with SO independently of the cause. It can be explained by the small population of our study.

Regarding age, most studies indicate that the age distribution for SO generally follows the average distribution of the general population, some report higher occurrence among children and individuals over 60 years of age, likely arising from increased ocular injury in young age and increased frequency of intraocular surgery in the older population [Erreur ! Source du renvoi introuvable.]. In this study, we found a higher occurrence among young patients due to penetrating injury and older patients due to intraocular surgery.

The reported interval between ocular injury and the onset of SO range from 5 days [Erreur ! Source du renvoi introuvable.] to 66 years [Erreur ! Source du renvoi introuvable.]. About 65% occurred within 2 weeks to 2 months after the injury and about 90% occurred within a year [Erreur ! Source du renvoi introuvable.][Erreur ! Source du renvoi introuvable.][Erreur ! Source du renvoi introuvable.]. Our cases are consistent with these findings. It varies from days to decades in our series. However, for 5 patients it occurred within a year following the scleral accidental or surgical trauma.

The general treatment principle observed is the initial aggressive control of the uveitis with systemic and topical CS followed by long-term step-wise use of CS-sparing immunosuppressive agents in the vast majority [Erreur ! Source du renvoi introuvable.]. High dose induction for 4 weeks followed by slowly dose tapering has been shown efficient in uveitis macular edema in a prospective way [25][26].

Indeed, there are frequent complications with the level and duration of CS therapy that may be required to control inflammation. Glaucoma and cataract are the commonest ocular problems related to periocular or intravitreal CS injections. Cataract has been reported in 20% at 6 months in eyes treated for uveitis with periocular CS injection [27]. Its incidence increases with the number of injections. Regarding steroid-induced glaucoma, it has been reported that 23% to 34% of patients with uveitis presented an intraocular pressure elevation over 24 mmHg with intraocular CS injection [27][28].

Others systemic side effects include hypertension, diabetes, osteoporosis and vertebral collapse, and may become the limiting factors in disease management.

For this reason, IS therapy is usually started for those with CS-dependence > 7.5 mg/d of prednisone in intend to reduce its dose and duration.

A step-wise escalation of multiple IS is employed when the first-line agent is insufficient as in suggested therapeutic algorithm for uveitic macular edema [29][30][31].

AZA and MMF are selective inhibitors of inosine-5-monophosphate dehydrogenase that is essential during the synthesis de novo of purines. They inhibit both T and B lymphocytes thus causing immunosuppression.

Wand K and al, reported the case of a patient with SO, treated with AZA, who improved his sympathizing eye BCVA from 0.6 to 0.9 logMAR [32].

In Hakin and al. study, the use of IS, such as cyclosporine and AZA, in combination with the CS, allows control of the intraocular inflammation at a much lower CS dose [33].

Tumor necrosis factor (TNF)- $\alpha$  is produced by T effector cells and macrophages, themselves activated by myeloid dendritic cells (DCs). In contrast, IFN- $\alpha$  is produced by plasmocytes dendritic cells (pDCs), mostly in response to viral infection. This response is necessary to control spread of virus but may also have implications for autoimmunity. [34]

The effectiveness of IFN- $\alpha$  therapy and of anti-TNF- $\alpha$  therapy in control of clinical and experimental autoimmune noninfectious uveitis implies a defect in regulation of autoreactive T-cells. In organ-specific autoimmune uveoretinitis, there may be a defect in pDCs function, either intrinsic or extrinsic, with a concomitant reduction in the pDCs' responsiveness to antigen challenge and impaired IFN- $\alpha$  production, particularly to viral challenge (CpG). This leads to a secondary defect in T-reg cell activation, with unrestrained autoreactive Th1-cell activation, which if the cross-reactivity matches, leads to autoimmune inflammation. It also explains the responsiveness of patients to IFN- $\alpha$  and to anti-TNF- $\alpha$  therapy based on low endogenous levels of IFN- $\alpha$  in these patients and a cross-regulatory function of TNF- $\alpha$  and IFN- $\alpha$  [34].

Lopez-Prats et al [35] reported a case of a good inflammation management in SO with ADA.

S.Gupta et al [36] reported a case of a 7-year-old diagnosed with SO. They had difficulties to taper CS doses using, in association or successively, cyclosporine, methotrexate and MMF.

They finally managed to taper and stop CS by introducing Infliximab (IFX). The randomized and prospective Visual 1 study [37] included 223 patients with intermediate and posterior non-infectious uveitis, and showed a significative longer delay of relapse of the uveitis for the patient with ADA versus placebos (24 weeks with ADA versus 13 weeks with placebo).

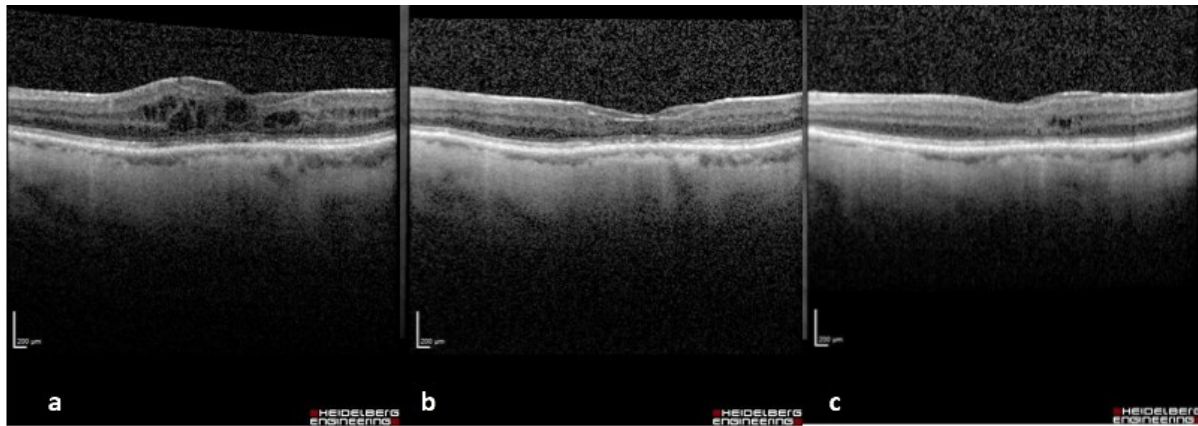
However, no significative effect on ME was found. In JF Arevalo et al [38] retrospective study over 25 years, 132 patients with Behcet disease-related uveitis were reviewed. 116 patients were treated by a various combination of IS therapy (cyclosporine, AZA, IFX, CS,



methotrexate) and only the combination of systemic CS, cyclosporine, and IFX demonstrated a significant improvement in BCVA ( $p= 0.032$ ).

Kilmartin et al [39] reported a case of a 3-year-old with SO who presented a complete resolution of a ME causing by an inflammatory-induced CNV, and an improvement of BCVA in 3 months with cyclosporine 5mg/kg per day. Hiyama et al [40] reported 2 cases of SO with serous retinal detachment (SRD). They first initiated cyclosporine but one SRD relapsed and the other patient presented side effect of the treatment leading to switch therapy for ADA which successfully resolved the SRD.

In Doycheva D, et al [41] study, upon 38 patients treated with MMF, CMT decreased for 12/24 patients with preexisting UME, but 14 patients with no history of UME before treatment, developed one. Other studies are more positive such as the Neri P. et al [42] study showing and improvement of UME at 1 year for 96% of the 19 patients with non-infectious chronic uveitis and ME treated with MMF. Cyclosporine at a nephrotoxic dose (5 and 10 mg/Kg/d), has been described as efficient on UME and has been used in numerous countries for more than 30 years for this purpose [43]. In the Schaap-fogler et al [44] study, upon 15 eyes treated with anti-TNF- $\alpha$  (IFX or ADA), 13 eyes achieved complete resolution of the UME and 2 showed partial improvement. 27 eyes received conventional treatment (CS, AZA, MMF, cyclosporine, methotrexate). The maximal reduction of CMT from baseline occurred at 6 months, in the anti-TNF- $\alpha$  group, reaching  $262\pm 73 \mu\text{m}$  ( $p=0.04$ ). At 12 months, the anti-TNF- $\alpha$  group showed a significantly greater reduction in CMT from baseline than the conventional-treatment group ( $304\pm 243 \mu\text{m}$  vs  $57\pm 227 \mu\text{m}$ ,  $p=0.03$ ). In the Mackensen et al study [45], IFN- $\alpha$  and beta have shown efficiency in refractory ME. In intermediate uveitis, the CFT mean decreased for  $206 \mu\text{m}$  with INF $\beta$  (44 $\mu\text{g}$ ), and increased for  $47\mu\text{m}$  with MTX (20mg/week) at 3 months ( $p < .0001$ ). The BIRDFERON study [25] showed a similar efficiency of systemic CS therapy and INF- $\alpha$ 2a alone at 4 months. The CFT mean decreased by  $63\mu\text{m}$  with INF- $\alpha$  and by  $52 \mu\text{m}$  with systemic CS and increased by  $3\mu\text{m}$  without treatment at 4 months. Moreover, the CFT mean of the eye with the worst BCVA, dropped by  $20 \mu\text{m}$  in the group with systemic CS and by  $155 \mu\text{m}$  in the group with INF- $\alpha$  suggesting an interest for refractory uveitic ME. Regarding UME in Behçet disease, the Calvo et al study [46], on 124 patients treated with IFX (64%) and ADA (38%) combined or not with conventional IS drugs, showed a significative improvement of the CFT, from  $420 \mu\text{m}$  (SD 119.5) at baseline to  $271 \mu\text{m}$  (SD 45.6) at month 12 ( $P < 0.01$ ) with a good control of endo-ocular inflammation and a significative improvement of the BCVA. **Figure 2** illustrates the effect of immunosuppressive therapy on macular edema for one patient of this study.



**Figure 2** – Interferon alpha2a effect on macular Edema on a 45 years old patient with sympathetic ophthalmia. Spectral Domain OCT images. a) Macular Edema before any immunosuppressive therapy. Edema persists with azathioprine and adalimumab. b) Reduction of the macular Edema with interferon alpha2a. c) Slow recurrence of the macular Edema 6 weeks after discontinuation of interferon alpha2a.

Another study reported that IFN- $\alpha$ 2a therapy had a beneficial effect on infectious UME for 100% of the 5 patients of the study. The results revealed that it was effective in 2 patients (3 eyes), effective dose-dependent in 2 patients, and partly effective in 1 patient [47].

Recently, based on the available evidence, an expert panel recommended that IFX and ADA (but not Etanercept) could be considered first-line immunomodulatory agents for the treatment of ocular manifestations of Behcet disease and in second-line immunomodulatory therapy for children with vision-threatening uveitis secondary to juvenile idiopathic arthritis in whom methotrexate therapy was insufficiently effective or not tolerated. They also recommended anti-TNF- $\alpha$  therapy for patients with panuveitis with vision-threatening, corticosteroid-dependent disease who failed first-line immunomodulatory therapies such as antimetabolites or calcineurin inhibitors [48]. Unlike conventional IS therapy and other biotherapy, IFN does not increase the infectious and carcinogenic risk that could be of interest in young people. Unfortunately, many side effects limit their use. The most common is the quasi-systematic flu-like syndrome, within hours of the injection. Psychiatric disorders (depression, anxiety, psychosis, suicide) are reported in 4 to 7.5% of patients. We have developed a closed psychological and ophthalmological care, allowing promptly adaptation of the therapeutic, avoiding severe psychological disturbances and preventing treatment discontinuation. The occurrence of cytopenia (mainly leukopenia), and endocrinological disturbances (mainly dysthyroidism) justifies regular monitoring [49].

Removal of the injured eye had been previously suggested at the time of injury, or soon after, in an attempt to prevent the development of SO [**Erreur ! Source du renvoi**

**introuvable.**].The postulated role of secondary enucleation of the exciting eye after the onset of symptoms of SO is to reduce the production of inflammatory mediators. It is also unclear whether enucleation of the exciting eye confers any benefit once disease has started in the sympathizing eye. Some feel that enucleation at this stage is valueless [**Erreur ! Source du renvoi introuvable.**][50] and should not be performed because the exciting eye may eventually have the better vision, or because the diagnosis of SO may be incorrect. Others state that enucleation within 2 weeks of onset of sympathetic inflammation is associated with a relatively benign clinical course, and improves visual outcome [**Erreur ! Source du renvoi introuvable.**][51].

In our study, 3 patients underwent enucleation, 1 year and 3 years after the outcome of SO. Two of three were sent to our tertiary for an inflammation rebound in the sympathetic eye following the enucleation.

In case of a painful exciting eye with no perception of light, a retrobulbar injection of mixed alcohol 60% and Xylocaïne 2% could be useful. If needed, a therapeutic contact lens, a scleral cover shell prosthesis or a surgical conjunctival flap can also be proposed.

Therefore, the decision for enucleation should be made very cautiously.

There are a few limitations in our study. It is a small monocentric retrospective series that leads to bias in data collection. Moreover, SO diagnosis is difficult in a late case. Incidence of SO, much of current literature is made up of case reports and small case series.

## **CONCLUSION**

SO is a potentially sight-threatening disease with high rates of visual loss. Multiple combination of immunosuppressive therapy had been tried. IFN- $\alpha$  and antimetabolites seemed to be the more effective to control inflammation, to resolve chronic macular edema, and steroid sparing. Enucleation of inciting eye seemed to have been pejorative in uveitis course in that small series. As far as we know, it is the first series of SO treated with IFN- $\alpha$  in the literature. A study with a larger sample size is needed to verify this hypothesis. It might be useful for an international consensus to establish and provide clarity in the treatment framework for patients with SO.

## **BIBLIOGRAPHY**

- 1) Gass JD. Sympathetic ophthalmia following vitrectomy. *Am J Ophthalmol.* 1982 May;93(5):552-8.
- 2) Kilmartin DJ, Dick AD, Forrester JV. Prospective surveillance of sympathetic ophthalmia in the UK and Republic of Ireland. *Br J Ophthalmol.* 2000 Mar;84(3):259-63.
- 3) Mackenzie W. *A Practical Treatise on the Diseases of the Eye.* Longman, Brown, Green & Longmans; 1854.
- 4) Fuchs E. Über sympathisierende Entzündung (nebst Bemerkungen über seröse traumatische Iritis). *Albrecht von Graefes Archiv für Ophthalmologie.* 1905 Sep;61(2):365-456.
- 5) Dalen A. Zur Kenntnis der sogenannten Choroiditis sympathetica. *Mitt Augen Klin Carolin Med. Chirurg Inst Stockholm.* 1904;6:1.
- 6) Duke-Elder SP. *System of ophthalmology volix: diseases of the uveal tract.*
- 7) Rao NA, Wong VG. Aetiology of sympathetic ophthalmitis. *Trans Ophthalmol Soc U K.* 1981 Sep;101 (Pt 3)(3):357-60.
- 8) Chu XK, Chan CC. Sympathetic ophthalmia: to the twenty-first century and beyond. *J Ophthalmic Inflamm Infect.* 2013 Jun 1;3(1):49.

- 9) Winter FC. Sympathetic Uveitis\*: A Clinical and Pathologic Study of the Visual Result. *American journal of ophthalmology*. 1955 Mar;39(3):340-7.
- 10) Trusko B, Thorne J, Jabs D, Belfort R, Dick A, Gangaputra S, Nussenblatt R, Okada A, Rosenbaum J; Standardization of Uveitis Nomenclature (SUN) Project. The Standardization of Uveitis Nomenclature (SUN) Project. Development of a clinical evidence base utilizing informatics tools and techniques. *Methods Inf Med*. 2013;52(3):259-65, S1-6.
- 11) Nussenblatt RB, Palestine AG, Chan CC, Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. *Ophthalmology*. 1985 Apr;92(4):467-71
- 12) Arevalo JF, Garcia RA, Al-Dhibi HA, Sanchez JG, Suarez-Tata L. Update on sympathetic ophthalmia. *Middle East Afr J Ophthalmol*. 2012 Jan;19(1):13-21.
- 13) Tan XL, Seen S, Dutta Majumder P, Ganesh SK, Agarwal M, Soni A, Biswas J, Aggarwal K, Mahendradas P, Gupta V, Ling HS, Teoh S, Pavesio C, Agrawal R. Analysis of 130 Cases of Sympathetic Ophthalmia - A Retrospective Multicenter Case Series. *Ocul Immunol Inflamm*. 2019;27(8):1259-1266.
- 14) Chang GC, Young LH. Sympathetic ophthalmia. *Semin Ophthalmol*. 2011 Jul-Sep;26(4-5):316-20.
- 15) Galor A, Davis JL, Flynn Jr HW, Feuer WJ, Dubovy SR, Setlur V, Kesen MR, Goldstein DA, Tessler HH, Ganelis IB, Jabs DA. Sympathetic ophthalmia: incidence of ocular complications and vision loss in the sympathizing eye. *American journal of ophthalmology*. 2009 Nov;148(5):704-10.
- 16) Gupta V, Gupta A, Dogra MR. Posterior sympathetic ophthalmia: a single centre long-term study of 40 patients from North India. *Eye*. 2008 Dec;22(12):1459-64.
- 17) Holland G. Ueber Indikation und zeitpunkt der Entfernung eines verletzten Auges. *Klin Monatsbl Augenheilkd*. 1964;145:732-40.
- 18) Su DH, Chee SP. Sympathetic ophthalmia in Singapore: new trends in an old disease. *Graefes Arch Clin Exp Ophthalmol*. 2006 Feb;244(2):243-7.
- 19) Liddy L, Stuart J. Sympathetic ophthalmia in Canada. *Can J Ophthalmol*. 1972 Apr;7(2):157-9. PMID: 4274314.
- 20) Albert DM, Diaz-Rohena R. A historical review of sympathetic ophthalmia and its epidemiology. *Survey of ophthalmology*. 1989 Jul;34(1):1-4.
- 21) Lubin JR, Albert DM, Weinstein M. Sixty-five years of sympathetic ophthalmia: a clinicopathologic review of 105, cases (1913–1978). *Ophthalmology*. 1980 Feb;87(2):109-21.
- 22) Zaharia MA, Lamarche J, Laurin M. Sympathetic uveitis 66 years after injury. *Can J Ophthalmol*. 1984 Aug;19(5):240-3.

- 23) Goto H, Rao NA. Sympathetic ophthalmia and Vogt-Koyanagi-Harada syndrome. *International ophthalmology clinics*. 1990 Oct;30(4):279-85.
- 24) Chan CC, Roberge FG, Whitcup SM, Nussenblatt RB. 32 cases of sympathetic ophthalmia: a retrospective study at the National Eye Institute, Bethesda, Md, from 1982 to 1992. *Archives of Ophthalmology*. 1995 May;113(5):597-600.
- 25) Fardeau C, Simon A, Rodde B, Viscogliosi F, Labalette P, Looten V, Tézenas du Montcel S, LeHoang P. Interferon-alpha2a and Systemic Corticosteroid in Monotherapy in Chronic Uveitis: Results of the Randomized Controlled BIRDFERON Study. *Am J Ophthalmol*. 2017 May;177:182-194.
- 26) Kempen JH, Altaweel MM, Holbrook JT, Jabs DA, Louis TA, Sugar EA, Thorne JE, Multicenter Uveitis Steroid Treatment (MUST) Trial Research Group, Writing Committee. Randomized comparison of systemic anti-inflammatory therapy versus fluocinolone acetonide implant for intermediate, posterior, and panuveitis: the multicenter uveitis steroid treatment trial. *Ophthalmology*. 2011 Oct;118(10):1916-26.
- 27) Sen HN, Vitale S, Gangaputra SS, Nussenblatt RB, Liesegang TL, Levy-Clarke GA, Rosenbaum JT, Suhler EB, Thorne JE, Foster CS, Jabs DA, Kempen JH. Periocular corticosteroid injections in uveitis: effects and complications. *Ophthalmology*. 2014 Nov;121(11):2275-86.
- 28) Lowder C, Belfort R Jr, Lightman S, Foster CS, Robinson MR, Schiffman RM, Li XY, Cui H, Whitcup SM; Ozurdex HURON Study Group. Dexamethasone intravitreal implant for noninfectious intermediate or posterior uveitis. *Arch Ophthalmol*. 2011 May;129(5):545-53.
- 29) Fardeau C, Champion E, Massamba N, LeHoang P. Uveitic macular edema. *Eye (Lond)*. 2016 Oct;30(10):1277-1292.
- 30) Koronis S, Stavarakas P, Balidis M, Kozeis N, Tranos PG. Update in treatment of uveitic macular edema. *Drug Des Devel Ther*. 2019 Feb 19;13:667-680.
- 31) Massa H, Pipis SY, Adewoyin T, Vergados A, Patra S, Panos GD. Macular edema associated with non-infectious uveitis: pathophysiology, etiology, prevalence, impact and management challenges. *Clinical Ophthalmology (Auckland, NZ)*. 2019;13:1761.
- 32) Wand K, Straub M, Lohmann CP, Mayer CS. Sympathische Ophthalmie. *Der Ophthalmologe*. 2016 Oct;113(10):867-9.
- 33) Hakin KN, Pearson RV, Lightman SL. Sympathetic ophthalmia: visual results with modern immunosuppressive therapy. *Eye*. 1992 Sep;6(5):453-5.
- 34) Plskova J, Greiner K, Muckersie E, Duncan L, Forrester JV. Interferon- $\alpha$ : a key factor in autoimmune disease?. *Investigative ophthalmology & visual science*. 2006 Sep;47(9):3946-50.

- 35) López-Prats MJ, Salom D, Sanz-Marco E, García-Delpech S, Udaondo P, Díaz-Llopis M. Terapia biológica en oftalmía simpática refractaria a tratamiento inmunosupresor combinado. *Archivos de la Sociedad Española de Oftalmología*. 2011 Jul;86(7):222-3.
- 36) Gupta SR, Phan IT, Suhler EB. Successful treatment of refractory sympathetic ophthalmia in a child with infliximab. *Archives of Ophthalmology*. 2011 Feb 14;129(2):250-2.
- 37) Jaffe GJ, Dick AD, Brézin AP, Nguyen QD, Thorne JE, Kestelyn P, Barisani-Asenbauer T, Franco P, Heiligenhaus A, Scales D, Chu DS. Adalimumab in patients with active noninfectious uveitis. *New England Journal of Medicine*. 2016 Sep 8;375(10):932-43.
- 38) Arevalo JF, Lasave AF, Al Jindan MY, Al Sabaani NA, Al-Mahmood AM, Al-Zahrani YA, Al Dhibi HA, Al-Dhibi HA, Al Shamsi HN, Al Suliman SM, Al Shamrani MA. Uveitis in Behçet disease in a tertiary center over 25 years: the KKESH Uveitis Survey Study Group. *American journal of ophthalmology*. 2015 Jan;159(1):177-84.
- 39) Kilmartin DJ, Forrester JV, Dick AD. Cyclosporine-induced resolution of choroidal neovascularization associated with sympathetic ophthalmia. *Archives of Ophthalmology*. 1998 Feb;116(2):249-50.
- 40) Hiyama T, Harada Y, Kiuchi Y. Effective treatment of refractory sympathetic ophthalmia with glaucoma using adalimumab. *American journal of ophthalmology case reports*. 2019 Jun;14:1-4.
- 41) Doycheva D, Zierhut M, Blumenstock G, Stuebiger N, Deuter C. Mycophenolate mofetil in the therapy of uveitic macular edema—long-term results. *Ocular immunology and inflammation*. 2012 Jun;20(3):203-11.
- 42) Neri P, Mariotti C, Cimino L, Mercanti L, Giovannini A. Long-term control of cystoid macular oedema in noninfectious uveitis with Mycophenolate Mofetil. *International ophthalmology*. 2009 Jun;29(3):127-33.
- 43) Nussenblatt RB, de Smet MD, Rubin B, Freidlin V, Whitcup SM, Davis J, Herman D, Bloom JN, Sran PK, Witcher S, Palestine A. A masked, randomized, dose-response study between cyclosporine A and G in the treatment of sight-threatening uveitis of noninfectious origin. *American journal of ophthalmology*. 1993 May;115(5):583-91.
- 44) Schaap-Fogler M, Amer R, Friling R, Priel E, Kramer M. Anti-TNF- $\alpha$  agents for refractory cystoid macular edema associated with noninfectious uveitis. *Graefe's Archive for Clinical and Experimental Ophthalmology*. 2014 Apr;252(4):633-40.
- 45) Mackensen F, Jakob E, Springer C, Dobner BC, Wiehler U, Weimer P, Rohrschneider K, Fiehn C, Max R, Storch-Hagenlocher B, Becker MD. Interferon versus methotrexate in intermediate uveitis with macular edema: results of a

- randomized controlled clinical trial. *American journal of ophthalmology*. 2013 Sep;156(3):478-86.
- 46) Calvo-Río V, Blanco R, Beltrán E, Sánchez-Bursón J, Mesquida M, Adán A, Hernandez MV, Hernandez Garfella M, Valls Pascual E, Martínez-Costa L, Sellas-Fernández A. Anti-TNF- $\alpha$  therapy in patients with refractory uveitis due to Behçet's disease: a 1-year follow-up study of 124 patients. *Rheumatology*. 2014 Dec;53(12):2223-31.
- 47) Qian Z, Fardeau C, Cardoso JN, Jellab B, Fan X, LeHoang P. Effect of interferon  $\alpha$ 2a in cystoid macular edema due to intraocular infection. *European journal of ophthalmology*. 2015 Sep;25(5):431-6.
- 48) Levy-Clarke G, Jabs DA, Read RW, Rosenbaum JT, Vitale A, Van Gelder RN. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. *Ophthalmology*. 2014 Mar;121(3):785-96.
- 49) Feurer E, Bielefeld P, Saadoun D, Sève P. Uvéïtes et biothérapies. *La Revue de Médecine Interne*. 2015 Feb;36(2):107-16.
- 50) IRVINE R. Sympathetic ophthalmia: a clinical review of sixty-three cases. *Archives of Ophthalmology*. 1940 Jul;24(1):149-67.
- 51) Reynard M, Shulman IA, Azen SP, Minckler DS. Histocompatibility antigens in sympathetic ophthalmia. *American journal of ophthalmology*. 1983 Feb;95(2):216-21.





## SERMENT D'HIPPOCRATE

Au moment d'être admis à exercer la médecine, en présence des maîtres de cette école et de mes condisciples, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité qui la régissent.

Mon premier souci sera, de rétablir, de préserver ou de promouvoir la santé dans tous les éléments physiques et mentaux, individuels collectifs et sociaux. Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions.

J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou dignité.

Même sous la contrainte, je ne ferai usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients de décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer leurs consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera.

Je ne me laisserai influencer ni par la recherche du gain ni par la recherche de la gloire.

Admis dans l'intimité des personnes, je tairai les secrets qui me sont confiés.

Reçu à l'intérieur des maisons, je respecterai les secrets des foyers.

Et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances, sans acharnement.

Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission.

Que je sois modéré en tout, mais insatiable de mon amour de la science.

Je n'entreprendrai rien qui ne dépasse mes compétences ; je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses,

Que je sois déshonoré et méprisé si j'y manque.