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Incidence, progression and risk factors for epiretinal membranes in the elderly: the ALIENOR study

Caroline Morillon

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THESE
Pour l'obtention du
DIPLOME D'ETAT DE DOCTEUR EN MEDECINE
U.F.R. des sciences médicales
Discipline : Ophtalmologie

Présentée et soutenue publiquement

Le 12 octobre 2018

Par Caroline MORILLON

Née le 20/11/1990 à Royan

**INCIDENCE, PROGRESSION AND RISK FACTORS FOR
EPIRETINAL MEMBRANES IN THE ELDERLY : THE ALIENOR
STUDY**

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Madame le Professeur Marie-Noëlle DELYFER

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Président :

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Juges :

Madame le Professeur Marie-Noëlle DELYFER

Monsieur le Professeur Jean-François DARTIGUES

Monsieur le Professeur David TOUBOUL

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Madame le Docteur Marie-Bénédicte ROUGIER

Rapporteur de Thèse :

Monsieur le Professeur Vincent SOLER

REMERCIEMENTS

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LISTE DES ABREVIATIONS

ALIENOR : Anti-oxydants, Lipides Essentiels, Nutrition et maladies Oculaires

3C : 3 cités

BMES : Blue Montain Eye Study

BMI : body mass index

CI : confidence interval

CI-5 : cumulative five-year incidence

CMR : cellular macular reflex

DBP : diastolic blood pressure

DMLA : dégénérescence maculaire liée à l'âge

DONFL : dissociated optic nerve fiber layer

DPV : décollement postérieur du vitré

EDI : enhanced depth imaging

ERM : epiretinal membrane

HR : hazard ratio

IR : incidence rate

MER : membrane épirétinienne

OCT : tomographie en cohérente optique. Optical coherence tomography

PMF : premacular fibrosis

SBP : systolic blood pressure

SD : standard deviation

SD-OCT : spectral domain optical coherence tomography

SFCT : subfoveal choroidal thickness

VMA : vitreomacular adherence

VPA : vitreopapillary adherence

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I INTRODUCTION

I.1 L'ETUDE ALIENOR

L'étude ALIENOR (anti-oxydant, lipides essentiels, nutrition et maladies oculaires), est une étude épidémiologique en population âgée basée sur l'analyse des pathologies oculaires liées à l'âge et leurs associations avec certains facteurs nutritionnels, génétiques, vasculaires et environnementaux.

Les participants ont été recrutés via l'étude épidémiologique des 3-cités (3C), conduite pour étudier la relation entre facteurs vasculaires et démence. 9294 participants tirés des listes électorales et âgés de plus de 65 ans ont été inclus entre 1999 et 2001 dans la cohorte 3C, dans les villes de Bordeaux, Montpellier et Dijon, puis réévalués tous les deux ans (1). De nombreuses informations étaient relevées au cours d'un entretien individuel tels que les données sociodémographiques, les antécédents médicaux, les habitudes alimentaires... Des mesures anthropométriques, la mesure de la tension artérielle ainsi qu'un bilan biologique comprenant notamment un dépistage du diabète et des dyslipidémies venaient clôturer cette évaluation.

Au 3ème suivi (2006-2008), un bilan ophtalmologique a été proposé aux 1450 participants bordelais : 963 ont accepté de participer à la première évaluation de l'étude ALIENOR (2). Celle-ci comprenait un recueil des antécédents ophtalmologiques, la mesure de l'acuité visuelle, un examen à la lampe à fente avec mesure du break-up time, de la pression intraoculaire, ainsi que la réalisation de rétinophotographies couleurs. Ces examens ont été réitérés environ tous les deux ans, avec l'ajout depuis 2009 d'un examen en tomographie à cohérence optique (OCT), d'une autofluorescence, de rétinophotographies grand champ, d'une mesure de la mesure de la longueur axiale, ainsi que l'étude des propriétés biomécaniques cornéennes.

Grace à ce bilan ophtalmologique complet, plusieurs affections ophtalmologiques affectant les personnes âgées peuvent être dépistées telles que la dégénérescence maculaire liée à l'âge (DMLA) ou encore le glaucome. En parallèle, le recensement de multiples paramètres généraux rend possible l'étude de nombreux facteurs de risques potentiels. La répétition des examens tous les deux ans, avec à ce jour cinq suivis complets depuis 2006, permet d'évaluer

l'incidence de ces pathologies ainsi que leur évolutivité, comme effectué récemment pour la DMLA (3).

Certaines associations ont pu être déjà démontrées et largement reconnues. Le tabac et certaines caractéristiques génétiques (variant Y402H du facteur H du complément, présence du gène ARMS2) ont été authentifiés comme facteurs de risques de la dégénérescence maculaire lié à l'âge (4, 5). L'apparition de celle-ci semble néanmoins réduite par une alimentation riche en oméga-3 (6).

Les pathologies de l'interface vitréo-rétinienne ont été jusqu'à présent peu étudiées au sein de la cohorte ALIENOR. Motif courant de consultation, nous avons choisi d'évaluer la présence de membrane épirétinienne chez les participants ainsi que leur évolutivité au cours des suivis.

I.2 LES MEMBRANES EPIRETINIENNES

Les membranes épirétiniennes (MER) sont des anomalies fréquentes de l'interface vitréoretinienne chez les sujets de plus de 50 ans (7). Majoritairement idiopathiques, elles peuvent aussi être secondaires à diverses affections comme le diabète, les uvéites, les occlusions veineuses ou encore les traumatismes oculaires (8).

Elles sont caractérisées par une prolifération cellulaire anormale à la surface rétinienne, composée de cellules gliales rétinienne (cellules de Müllers, astrocytes et microglies), hyalocytes, cellules de l'épithélium pigmentaire, fibroblastes et myofibroblastes (9, 10). Les cellules gliales seraient la composante essentielle des MER idiopathiques (11).

La physiopathologie de ces dernières est encore imparfaitement comprise. Le décollement postérieur du vitré (DPV) pourrait être à l'origine de micro-trous dans la limitante interne, responsables d'une prolifération de cellules gliales rétinienne à travers ces orifices (9, 12-14). Un schisis de la hyaloïde postérieure avec résidus de cortex vitréen à la surface rétinienne lors d'un DPV pathologique pourrait aussi induire la formation de ces membranes (expliquant ainsi la présence de hyalocytes dans leur composition) (15, 16). Certains facteurs de risques ont été identifiés, comme l'âge et la chirurgie de la cataracte (17-24).

Les MER peuvent être à l'origine de métamorphopsies, micropsies, et baisse d'acuité visuelle plus ou moins marquée selon leur caractère contractile. D'évolution lente, elles peuvent aussi être découvertes de manière fortuite et rester asymptomatiques (25, 26). On les trouve

fréquemment séparées en deux stades dans la littérature, à partir de l'aspect du fond d'œil ou des retinophotographies, selon la classification de Klein et al. (17). Le stade « cellophane macular reflex » correspond à un reflet brillant cellophane s'étendant au pôle postérieur sans plis rétiens. Le stade « premacular fibrosis » est un stade plus mature, accompagné de plis rétiens et inconstamment de déformation des arcades vasculaires.

Depuis sa création en 1991, l'OCT est devenu l'outil de référence dans l'étude des pathologies maculaires. Rapide et non invasif, il permet d'obtenir des images de hautes définitions de l'interface vitréorétinienne (27). Les MER apparaissent comme des fines lignes hyper-réfléctives prérétiennes, pouvant être détectées plus précocement que sur les retinophotographies, notamment en cas de cataracte débutante (28). Il n'existe pas de classification de référence des MER à partir de l'OCT. Nous avons donc établi notre propre classification pour affiner le diagnostic de MER des participants de l'étude ALIENOR. Celle-ci définit 3 stades évolutifs : le stade 1, précoce, avec une hyperréfléctivité prérétinienne isolée ; le stade 2, intermédiaire, associant le stade 1 à la présence de plis rétiens ; et le stade 3, final, ajoutant la modification de la dépression fovéolaire aux plis rétiens (**figure 1**). Plusieurs études épidémiologiques ont déjà été réalisées, portant majoritairement sur la prévalence (17-24, 29-36). Seules trois études d'incidence des MER existent, basées uniquement sur les retinophotographies, retrouvant une incidence cumulée entre 3.8% et 8.4% (37-39).

Nous avons donc décidé de réaliser la première étude d'incidence des MER à partir de l'OCT et de rechercher les facteurs de risque potentiels au sein de la cohorte ALIENOR.

II ARTICLE

Incidence, progression and risk factors for epiretinal membranes in the elderly: the ALIENOR study

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Abbreviated title: *Epiretinal membrane in the Elderly*

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Key words: cumulative incidence, epidemiologic study, elderly subjects, epiretinal membrane, eye aging, incidence rate, general population, population-based study, progression rate, risk factors

Summary statement:

ERM incidence in the elderly was studied using for the first time SD-OCT images. ERM incident rate was higher than previously described, due to the higher sensitivity of SD-OCT as compared to color photographs. Risk factors independently associated with ERM were cataract surgery, vitreous adhesion, smoking and, interestingly, choroidal thinning.

II.1 ABSTRACT

Purpose: To determine the incidence, progression rate and risk factors for epiretinal membranes (ERMs) in a population of French elderly subjects.

Methods: 735 eyes of 413 participants of the ALIENOR study were included between 2009 and 2010. Participants were reevaluated every two-years between 2009 and 2017 (corresponding to 3 follow-up visits). All included eyes had gradable spectral-domain optical coherence tomography (SD-OCT), retinal images at baseline and at least one follow-up data collection point. A classification of ERMs using SD-OCT findings was set up to evaluate ERM incidence and progression.

Results: The incidence rate of ERM was 9.42 per 100 eye-years (95% confidence interval (CI), 7.36-12.05) in our population, corresponding to a five-year cumulative incidence of 37.57%. ERM incidence was significantly associated with smoking after 85 years (Hazard Ratio (HR), 4.81; $p=0.022$), cataract surgery (HR, 1.86; $p=0.0108$), presence of vitreomacular or vitreopapillary adhesion (HR, 1.64; $p=0.038$) and decrease in choroidal thickness (HR 1.04; $p=0.0094$). The five-year cumulative progression rate was 6.86%.

Conclusion: Due to the systematic use of SD-OCT images, early ERMs were found to be far more frequent in our population than previously described. Incident ERMs were associated with three main ocular risk factors: cataract surgery, vitreous adhesion and interestingly, choroidal thickness.

II.2 INTRODUCTION

Epiretinal membranes (ERM) are a relatively common disorder of the vitreo-macular interface, characterized by a proliferation of fibrocellular and avascular tissue on or above the surface of the macula. They can exhibit retractile properties that, eventually, can lead to a distortion of macular inner retinal layers. ERM usually progress slowly over time, and often remain stationary for long time periods (1-4). Functionally, patients with ERM can either stay asymptomatic or experience blurred vision and/or metamorphopsia, depending on the severity of macular distortion. On fundus examination, ERM are seen as a crinkled cellophane aspect of the macula (5). Yet, early clinical detection of ERM remains difficult in some cases. The imaging of the vitreo-retinal interface using spectral domain OCT (SD-OCT) thus represents a key-element to assess ERM diagnosis. On SD-OCT images, ERM appear as a highly reflective layer along the surface of the inner limiting membrane that can be associated with retinal folds and/or foveal depression alterations according to its severity. SD-OCT further allows precise follow-up and proper management (6-8).

ERM can be secondary to another disease, such as diabetes, ocular surgery, uveitis, vein occlusion, or ocular trauma. But, in other cases, ERM may occur without any identified predisposing pathology, and are hence referred as “primary” or “idiopathic” (9). Several clinical and histopathologic studies have been conducted to improve our understanding of the pathogenesis of idiopathic ERM. Posterior vitreous detachment (PVD) and aging have been shown to play a decisive role in their occurrence (1, 10-12). However, beyond these two risk factors, the precise cellular mechanisms underlying primary ERM formation remain to be identified. Two hypotheses have been proposed in the literature. Some authors consider ERM to be of retinal origin, resulting from the migration of retinal cells through a defect in the inner limiting membrane secondary to PVD (2, 13-15). Alternatively, ERM could derive from the vitreous; in this case, an abnormal stretching of the posterior vitreous during PVD may result in some residual vitreous tissue remaining attached to the macula and ultimately evolving into a mature ERM (16, 17).

Epidemiological studies on ERM have mainly focused on their risk factors and prevalence. Most studies have confirmed the positive association with increasing age, and further found an association with cataract surgery (18-25). Prevalence of ERM has been analyzed across different population groups, and found to range between 2.2% and 34.1% (18-33). The highest prevalence rate was observed in the Beaver Dam Eye Study (6), possibly because of the systematic use of SD-OCT for ERM diagnosis, whereas most of the other

studies only analyzed fundus color images for ERM grading. As for the incidence rate of ERM, it has been poorly studied in the general population. The Blue Mountain Eye Study (BMES) and a Korean study have analyzed ERM incidence, with a five-year cumulative rate of 5.3% and 3.8%, respectively (34, 35). More recently, the Beijing Eye Study (BES) has reported a ten-year cumulative incidence rate of 8.4% (36). Yet, in all of these three studies, ERM diagnosis was only based on stereoscopic retinal photograph analyses, which may have caused early ERM cases to go under-detected.

The purpose of this study is therefore to assess ERM incidence in a population-based study of French elderly subjects using for the first time SD-OCT images, to analyze the progression of incident ERM during follow-up, to study the associated potential risk factors, and, finally, to evaluate the overall evolution of both preexisting and incident ERM in our entire population.

II.3 METHODS

II.3.1 Study participants

The ALIENOR (*Antioxydants, Lipides Essentiels, Nutrition et maladies Oculaires*) Study is a prospective population-based study aiming at assessing the associations of age-related eye diseases with nutritional factors. It also takes into account other major determinants of eye diseases, including gene polymorphisms, lifestyle and vascular risk factors.

Subjects of the ALIENOR study were recruited from the 3C Study, an ongoing population-based study focusing on the vascular risk factors for dementia. The 3C Study included 9294 subjects aged 65 years or more from three French cities (Bordeaux, Dijon and Montpellier), among whom 2104 were recruited in Bordeaux. Subjects were contacted individually from the electoral rolls. They were initially recruited in 1999-2001 and followed-up about every two years thereafter. The ALIENOR study per se consists in periodic eye examinations proposed to all participants since the third follow-up (2006-2008) of the 3C cohort of Bordeaux. Among the 1450 participants of the 3C Study re-examined in 2006-2008, 963 (66.4%) participated in the ALIENOR study. Detailed characteristics of participants and nonparticipants have been described elsewhere (37). In our study, we used the fourth follow-

up of the 3C study as baseline (2009-2010), as SD-OCT examinations of the macula and of the optic nerve were systematically included from then on. Among the 904 ALIENOR study participants still alive, 624 (69.2 %) participated in this eye examination. Every follow-up examinations thereafter were included in this study: 2009-2010 (baseline: wave 1; Alienor 1), 2011-2012 (first follow-up visit: wave 2; Alienor 2), 2013-2015 (second follow-up visit: wave 3; Alienor 3), and 2015-2017 (third follow-up visit: wave 4; Alienor 4).

This research followed the tenets of the Declaration of Helsinki. Participants gave written consent for participation in the study. The design of the ALIENOR study has been approved by the Ethical Committee of Bordeaux (Comité de Protection des Personnes Sud-Ouest et Outre-Mer III) in May 2006.

II.3.2 Eye examination

All eye examinations were performed in the Department of Ophthalmology of the University Hospital of Bordeaux, and included: recording of past ophthalmological history, measurement of refraction by an auto-refractometer (Speedy-K, Luneau, Prunay-le-Gillon, France), best-corrected visual acuity (using Early Treatment Diabetic Retinopathy Study (ETDRS) scale), intraocular pressure measurement with a non-contact tonometer (KT 800, Kowa, Tokyo, Japan), slit lamp examination, non-mydratic color images of the macula and the optic disk (TRC NW6S; Topcon, Tokyo, Japan), axial length measurement with non-contact partial coherence laser interferometry (IOL Master; Carl Zeiss Meditec AG, Jena, Germany), and SD-OCT examination (Spectralis®, Heidelberg Engineering, Heidelberg, Germany).

II.3.3 SD-OCT imaging

SD-OCT examinations were performed using Spectralis® OCT (Software Version 5.4.7.0; Heidelberg Engineering, Heidelberg, Germany). All OCT assessments were performed by the same experienced technician without pupil dilation. For macular cube acquisition, conditions used for acquisition were the following: resolution mode, high speed; scan angle, 20°; size X, 1024 pixels (5.7 mm); size Z, 496 pixels (1.9 mm); scaling X, 5.54 µm/pixel; scaling Z, 3.87 µm/pixel; number of B-scans, 19; pattern size, 20 × 15° and distance between B-scans, 236 µm. Standard horizontal and vertical B-scan images centered on the fovea, horizontal B-scan crossing the fovea using the Enhanced Depth Imaging (EDI) and OCT-scans focused on the optic nerve head were also performed. SD-OCT images from each follow-up were interpreted by a trained ophthalmologist. Presence of epiretinal membrane (ERM), vitreomacular

adhesion (VMA) and vitreo-papillary adhesion (VPA) were systematically graded. Subfoveal choroidal thickness (SFCT) was measured manually, on one horizontal OCT B-scan crossing the fovea and acquired using the EDI mode, between the retinal pigment epithelium and the outer choroidoscleral boundary as previously described (38).

II.3.4 Classification of ERM

On SD-OCT, ERM appears as a continuous hyper-reflectivity at the inner surface of the retina, with or without a rippling of the retinal surface, and with or without an alteration of the foveal area. In the absence of a standardized OCT-based classification of ERMs applicable for epidemiological purposes, ERMs were graded in our study from OCT-scans as follows: i) *stage 0*: absence of continuous hyper-reflective signal at the inner retinal surface, ii) *stage 1 or continuous hyper-reflectivity*: presence of a continuous hyper-reflective signal at the inner retinal surface on at least three consecutive sections, iii) *stage 2 or mature ERM without foveal involvement*: stage 1 associated with retinal folds but without alterations of the foveal depression and, finally, iv) *stage 3 or mature ERM with foveal involvement*: stage 2 associated with foveal depression alterations (**figure 1**).

Incidence of ERMs was defined if a stage 1, 2 or 3 was newly found at any of the follow-up visits in eyes that had no sign of ERM (stage 0) at baseline (wave 1; ALIENOR 1; 2009-2010).

Progression of ERMs was defined when a stage 1 at baseline became stage 2 or 3 at any of the follow-up visits.

II.3.5 Analysis of posterior vitreous cortex status on SD-OCT images

Presence of vitreo-macular adhesion (VMA) and vitreo-papillary adhesion (VPA) were assessed using macular and optic nerve SD-OCT images, respectively. According to the International Vitreomacular Traction Study (IVTS) classification, VMA was defined by an « elevation of the cortical vitreous above the retinal surface, with the vitreous remaining attached within a 3-mm radius of the fovea without retinal abnormalities » (39). Presence of VPA was established when posterior hyaloid was found to be attached to the optic disk.

II.3.6 Other Variables

During baseline home visit of the 3C study (1999-2001), all participants underwent a face-to-face interview using a standardized questionnaire, administered by a trained psychologist or nurse for the assessment of systemic risk factors. A systemic clinical examination included two measures of systolic and diastolic blood pressure using a digital electronic tensiometer (OMRON M4; Omron Santé France SAS, Rosny-sous-Bois, France) and anthropometric measurements. The first blood pressure measurement was recorded at the beginning of the interview and the second one at the end. The average systolic blood pressure (SBP) was the average of these two SBP measures. The same calculation was made for the average diastolic blood pressure (DBP). Hypertension was defined as average SBP \geq 140 mmHg and/or average DBP \geq 90 mmHg and/or antihypertensive medication use at baseline examination. The Body Mass Index (BMI; kg/m²) was calculated as the weight in kilograms divided by the height in square meters. Diabetes was defined as medication use and/or self-reported diabetes. For participants who were current or past smokers, the number of pack-years was calculated as: (number of smoking years) \times (mean number of cigarettes per day)/20. Hypercholesterolemia was defined by hypercholesterolemia medication. Past medical history including ophthalmic laser treatment or cataract surgery was recorded. Cataract extraction was checked during slit lamp examination.

II.3.7 Statistical analyses

Characteristics of eyes included in our study were compared with that excluded using logistic Generalized Estimating Equations (GEE) models, which allow taking into account the data from both eyes and their intra-individual correlations (40). For continuous variables, results were presented using means \pm standard deviations. For categorical variables, results were presented using n and percentage.

Incidence rate, progression rate and 95% confidence intervals (CIs) of ERM per eye were obtained using Poisson regression models for correlated data. The cumulative 5-year incidence (CI-5) was derived from the incidence rate (IR) using the following exponential formula (41): $CI-5(t) = 1 - \exp(-IR \times t)$.

Associations between ERM occurrence and other variables under study were estimated using Cox proportional hazards models with delayed entry and age as the time scale. Hazard ratios (HRs) and 95% CIs for occurrence of ERM were estimated using the individual eye as the unit of analysis (42). First, the association with each risk factor was assessed independently

using gender-adjusted models. Secondly, all factors found to be associated with a $p < 0.20$ were subjected to a multivariate model.

All statistical analyses were carried out using statistical software (SAS, version 9.4 SAS Institute, Inc., Cary, NC, USA), and $P < 0.05$ was considered statistically significant.

II.4 RESULTS

II.4.1 Study participants

Among the 1248 eyes of 624 participants at baseline, 168 eyes were not eligible for ERM incidence and progression analyses, since 136 had prevalent ERM (65 ERM stage 2, 71 ERM stage 3) and 32 had missing SD-OCT examinations. Of the remaining 1080 eyes, 166 did not participate in any follow-up examinations and 179 had some ungradable SD-OCT during follow-up. Finally, 735 remaining eyes were included: 378 eyes with ERM stage 0 for incidence analysis, and 357 eyes with ERM stage 1 for progression analysis. The mean duration of follow-up was 5.09 (SD, 1.8; range, 0.99-7.85). Comparison of demographic characteristics between included and non-included eyes of ALIENOR participants is summarized in **Table 1**. Included and non-included eyes differed for age (81.3 years and 83.4 respectively, $p < 0.0001$), for BMI (26.0 and 25.2 respectively, $p < 0.014$) and axial length (23.4 and 23.9 respectively, $p = 0.0002$). No statistically significant difference was found between the two groups regarding sex, education level, smoking status, diabetes, lens extraction, posterior vitreous cortex status (VMA or VPA) or laser eye treatment. At baseline, 45.9 % of included eyes were pseudophakic and 29.4% had VMA and/or VPA.

Concerning the evaluation of potential risk factors for ERM, among the 378 eyes eligible for ERM incidence analysis at baseline, 91 had missing data for risk factors assessment. Analyses on risk factors were therefore performed on 287 eyes.

Finally, in order to conduct an overall analysis of the evolution in ERM grading during the entire follow-up of the study, all eyes at baseline with follow-up data available were considered, i.e. not only the 378 eyes with ERM stage 0 and 357 eyes with ERM stage 1 described above, but also 111 eyes with ERM stage 2 ($n=55$) or 3 ($n=56$) at baseline. This last analysis was hence performed on 846 eyes.

II.4.2 Incidence and progression of ERM

The mean annual incidence rate of ERM per 100 eyes was 9.42 (95% confidence interval (CI), 7.36-12.05) as shown in **Table 2**. ERM incidence was significantly higher in women than in men (8.72 vs. 6.52; $p < 0.03$), and after 80 years of age (9.39 vs. 6.76; $p < 0.009$). The five-year cumulative incidence rate was 37.57%.

Among the 357 eyes with stage 1 ERM at baseline, only 20 of them disclosed a progression (1.142 per 100 eye-years; 95% CI, 0.88-2.30) (**Table 2**). ERM progression was significantly lower in women than in men (1.35 vs. 2.50; $p = 0.019$). The progression rate was lower after 80 years of age than before, but this difference did not reach statistical significance. The five-year cumulative progression rate was 6.86%.

II.4.3 Risk factors for incident ERM

After adjusting for age and sex, incident ERM was associated with past history of cataract surgery (Hazard Ratio (HR), 1.90; 95% CI, 1.18-3.07; $p = 0.0081$, **Table 3**). Increased choroidal thickness (10 μ m) was associated with a lower risk of incident ERM (HR, 0.96; 95% CI, 0.94-0.99; $p = 0.012$, **Table 3**) and this association remained statistically significant after adjusting for axial length ($p = 0.0055$). Presence of ERM stage 2 or 3 in the fellow eye at baseline was significantly associated with an increasing incidence of ERM in the studied eye (HR, 2.26; 95%CI, 1.06-4.81; $p = 0.042$, **Table 3**). Influence of smoking status on ERM incidence was not constant over the time, as a crossing point of survival curves was observed at 85 years. History of smoking was hence significantly associated with an increased ERM incidence after 85 years (HR, 4.85; 95% CI, 1.95-12.07; $p < 0.003$, **Table 3**), while it was not found to be significant before. There was no significant association between incident ERM and other measured parameters either ocular (VPA or VMA, prior ocular laser treatment) or systemic (BMI, diabetes, high blood pressure, antihypertensive treatment) (**Table 3**).

The multivariate analysis of risk factors for ERM incidence is presented in **Table 4**. Among systemic risk factors, only history of smoking in subjects older than 85 years was still significantly associated with ERM incidence (HR, 4.81; 95% CI, 1.91-12.11; $p < 0.003$).

Incident ERM remained strongly associated with past history of cataract surgery (HR, 1.86; 95% CI, 1.15-2.99; $p < 0.011$), while increased choroidal thickness still appeared protective (HR, 0.96; 95% CI, 0.94-0.99; $p = 0.0094$). Interestingly, in the multivariate model, presence of VPA or VMA at baseline was also significantly associated with incident ERM (HR, 1.64; 95% CI, 1.03-2.61; $p = 0.038$), confirming the clinical observation in some participants over

time. **Figure 2** shows the case of a subject with VPA and VMA at baseline who developed an incident ERM during follow-up.

II.4.4 Overall evolution in ERM grading during entire study

For this last analysis, as specified in the studied population section, all eyes with interpretable follow-up data were considered whatever ERM stage at baseline, i.e. not only ERM stage 0 (n=378) and stage 1 (n=357), but also stage 2 and stage 3 (n=111). **Figure 3** describes the overall evolution of ERM staging for each analyzed eye at baseline over the follow-up. 7.9% ERM stage 0 at baseline (95% CI, 6.1-10.2) were hence graded stage 1 at the most during the follow-up while only 0.8% (95% CI, 0.5-1.5) of stage 0 (n=13) reached stage 2 or 3. Among these last 13 eyes, 4 were graded during follow-up as stage 1 before reaching stage 2 or 3. 1.1% of ERM stage 1 reached stage 2 or 3 (95% CI, 0.7-1.8). 3.1% of ERM stage 1 (95% CI, 2.3-4.3) were graded stage 0 during the study. Only 0.4% (95%CI, 0.1-1.7) and 0.6% (95% CI, 0.2-2.0) of ERM stage 2 or 3 (n=5) evolved over the years respectively down to ERM stage 1 and 0. However, among these five cases, at least three ERMs were removed surgically according to participant's declaration (and confirmed by a dissociated optic nerve fiber layer (DONFL) aspect on OCT B-scans) (43, 44).

II.5 DISCUSSION

Our study is the first population-based study to estimate ERM incidence based on SD-OCT findings. In BMES (34), a Korean study (35) and very recently in BES (36), ERM incidence was only evaluated from retinal color images, which have been shown to be less accurate for ERM detection (45, 46), especially in early ERM cases. During the entire follow-up period of our study, ERM incidence rate hence was 9.42 per 100 eye-years (95% CI, 7.36-12.05). The corresponding five-year cumulative incidence rate was 37.57%, while it was only 5.3% and 3.8% in BMES and in the Korean study, respectively (34, 35). Discrepancies in these results could be due, first, to the underestimation of early ERM cases on color images as compared to SD-OCT scans. Indeed, in our cohort the five-year cumulative incidence rate of mature ERM (i.e. stages 2 and 3) was 5.4% (data not shown), a similar value to that observed

in the two other studies. Secondly, the use of five-year intervals between follow-up examinations – both in BMES and in the Korean study – may have led to survival bias and decreased incidence rates, as some participants may have developed ERM and died within the five-year interval and therefore would not be counted as incident cases. This is even more true for BES, which measured a ten-years cumulative incidence of ERM, with a value of 8.4%. Our much shorter intervals (1 to 2 years between examinations) has probably decreased much of this survival bias and may at least partly also explain the higher incidence rates we observed.

In our population, ERM incidence rate was found to be higher in person aged 80 years and older, and in women. In younger populations, the Korean study (35) and BMES (34) conversely observed that ERM -as diagnosed on color photographs- peaked at 60 year-old through 69, and decreased after 70 years (in a drastic way in the Korean study). In BES, the highest incidence rate of ERM was between 70 and 79 years old (36). The difference in our findings may be explained either by the genetic background of our participants and/or (and perhaps mainly) by the different protocols used for ERM diagnosis, SD-OCT versus retinal color images respectively, since with age lens opacities may impair ERM detection far more on retinal color images than on OCT B-scans. As for gender, none of the three previous incidental studies reported significant differences for ERM incidence rate (34-36). Women were however found to be more likely to exhibit ERM in three prevalent surveys (20, 24, 28).

Among considered systemic risk factors, history of smoking in subjects aged 85 years or more was found to be associated with an increased risk for ERM incidence (HR, 4.85; 95% CI, 1.95-12.07; $p < 0.003$, **Table 3**), while it was not observed before 85 years. In the literature, smoking was not identified as a risk factor for ERM in studies focusing on ERM incidence (35, 36) and was moderately associated with ERM in studies on ERM prevalence, but in this last case, mostly in a protective way (21, 25, 30, 32). The main reason for these discrepancies may be due to the age of the studied populations, since only smoking considered together with increasing age was found to be a risk factor in our cohort. Besides smoking, no other systemic risk factors (diabetes, blood hypertension, BMI) were found to be associated with ERM incidence in our population.

Among considered ocular risk factors, cataract surgery was found to be associated with incident ERM (HR, 1.86; CI, 1.15, 2.99; $p = 0.0108$). These results are similar to those recently observed in BES, and are in line with previous reports. In an observational clinical study, Fong and co-authors indeed studied the 3-year age-standardized ERM incidence after cataract surgery as compared to a BMES subsample of the same age range, and described a

three-fold higher ERM incidence after lens extraction (47). Another study analyzed ERM prevalence 6 month after cataract surgery as compared to postoperative day 10 findings. The prevalence increased from 14.8% to 25.3%, and this rise was significant (48). Since PVD was shown to occur in 71.4% of the patients within the three months following cataract surgery (49), anterior-posterior traction forces applied on the posterior vitreous cortex during surgery and resulting PVD were proposed as a risk factor for ERM (49, 50).

The great value of SD-OCT for vitreoretinal interface analysis is indisputable. The detached posterior vitreous cortex can easily be observed as a discrete linear signal above the retina on B-scans (51-55). Based on OCT findings, Uchino et al (56) defined five stages of posterior vitreous detachment (PVD), with a stage 3 described as a partial PVD with persistent adhesion to the optic nerve head, equivalent to VPA in our study. As for VMA, it was defined by the International Vitreomacular Traction Study Group as part of the natural course of PVD (39). Interestingly, in the multivariate model, we found a statistically significant association between presence of VPA or VMA at baseline and incident ERM during follow-up (HR, 1.64; CI, 1.03, 2.61; $p=0.038$). Considering that both VPA and VMA are identified steps of physiological PVD, it can therefore be assessed that ERM incidence is associated with PVD. These findings are consistent with numerous previous clinical studies (1-4, 10-13, 57) and, lately, with BES that showed a positive association of incident ERM with presence of a complete PVD (36).

SD-OCT through the use of EDI-mode further allows the evaluation of the choroid. Changes in choroidal thickness –and especially subfoveal choroidal thickness (SFCT)– were reported in several retinal conditions, bringing new pathophysiological insights on retinal diseases (58). In the present work, a protective association was observed for the first time between increased SFCT and incident ERM (HR, 0.96; CI, 0.94, 0.99; $p<0.01$). Yet, to our knowledge, no data are available at present in the literature to evaluate this result. Most clinical studies only focused on choroidal thickness modifications after vitrectomy for idiopathic ERM removal with controversial results (59-61). Some authors observed no significant choroidal differences in eye with ERM as compared to the fellow healthy eye (59, 61), others reported alterations of the choriocapillaris in eyes with ERM (i.e. decrease in flow area and parafoveal vessels density) as compared to contralateral eye, that resolved after surgery (62). Choroidal thickness was further found to decrease after vitreoretinal surgery (59-61).

Finally, presence of mature ERM in the contralateral eye at baseline (i.e. ERM stage 2 or 3 according to our classification) was significantly associated with incident ERM (HR,

2.26; CI 1.06, 4.81; $p=0.042$). This result is in line with clinical observations. In 1988, Appiah et al. indeed already reported the review of 324 idiopathic ERM cases with 19.1% of patients being affected in both eyes (4). This result is further confirmed by BMES data that showed a 2.5-fold increase in ERM incidence in the fellow eye (34). Recently, BES observed that incident ERM were bilateral in 25% of cases (36). This suggests that key background factors –either systemic or ocular– are determinant for ERM occurrence. However, this result was no longer present in the multivariate model, either due to a lack of power in our analysis or to interaction(s) with other factors.

Clinical studies demonstrated that most a- or pauci-symptomatic ERM exhibit a slow and moderate progression, and thus only require a clinical monitoring (1, 63). This was confirmed in our cohort with a mean annual progression rate per 100 eyes of 1.142 (95% CI, 0.88-2.30, **Table 2**) that corresponds to a five-year cumulative progression rate of 6.86%. In BMES, five-year progression from cellular macular reflex (CMR) to premacular fibrosis (PMF) as defined on retinal color images was higher, at 9.3%. In BES, 20 of the 64 eyes (31.3%) with pre-existing ERMs showed a progression from CMR to PMF or by increasing the ERM area by more than 25% (36). These two reported higher progression rates, as compared to our, could be due to a higher detection of early cases of ERM on SD-OCT images in our population that lowered the overall rate of progression. In our population, ERM progression was found to be significantly lower in women than in men (1.35 vs. 2.50; $p=0.019$) and tended to decrease with age. Influence of gender and age on progression rate was not evaluated in BMES or in the Korean study, no ocular or general parameters were found to be associated to progression in BES.

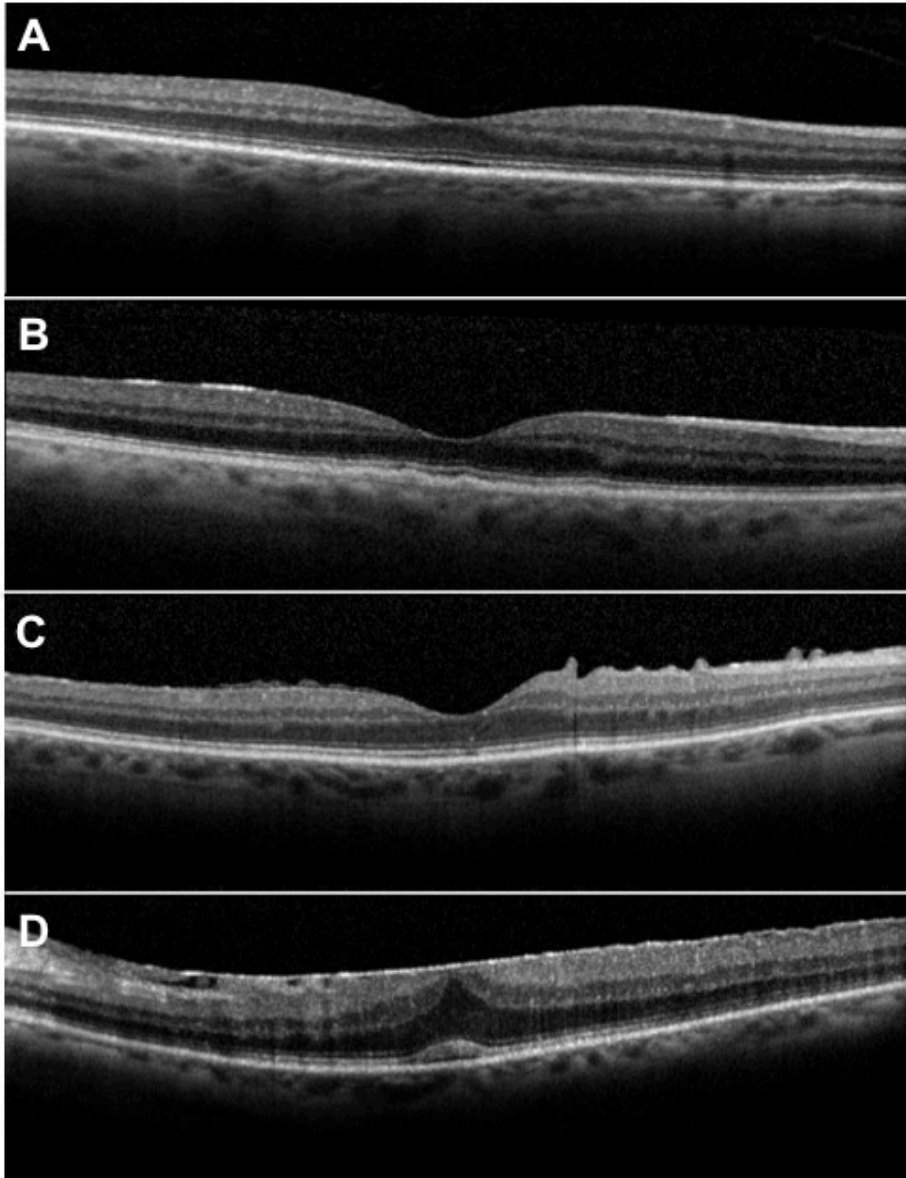
Still, our study has some limitations. First, this study was performed in a very elderly population (81.3 ± 3.8 years) and this could have induced either under or over-estimation of incidence and/or progression rates. Secondly, due to the lack of standardized OCT-based classification of ERM that could be applicable for epidemiological purposes, we had to set up our own classification. Whereas stages 0, 2 and 3 appear rather consensual, stage 1 – considered as the early stage of ERM– could be more questionable. Stage 1 was defined as the presence of a continuous hyperreflective signal at the inner retinal surface on at least three consecutive sections. One could wonder whether this continuous hyperreflective signal really represents early ERM or would be more likely to be due to posterior hyaloid reflection. As an attempt to limit confusion with posterior hyaloid reflectivity, we only retained in stage 1 the cases with continuous hyperreflectivity on at least three consecutive sections. We observed

that 7.9% of stage 0 rose up to stage 1 during follow-up. Only 0.8% (13 eyes) went from stage 0 at baseline to stage 2 or 3 during follow-up. Among these 13 eyes, four of them were identified as stage 1 at one intermediary follow-up visit. Incident ERM were then mostly stage 1. Since, on the one hand, risk factors for incident ERM were in line with the recent literature and, on the other hand, four eyes were graded as stage 1 before reaching stages 2 or 3, we deeply believe that stage 1 really represents an intermediary stage before stage 2 or 3 and that the observed hyperreflectivity is due to very early fibroglial cell proliferation. Nevertheless, whatever the stage considered, some subjects disclosed a descending evolution. 3.1% of ERM stage 1 at baseline were graded as stage 0 at least one time during the follow-up, 0.4% of stage 2 or 3 descended to stage 1 and 0.6% to stage 0. If minor variations could reflect grading mistakes due to the quality of OCT images or to the grader, the 3.1% of subjects who returned from stage 1 to stage 0 are more confusing. This could illustrate the possible spontaneous release of the beginning fibroglial proliferation. Self-resolution of ERM was indeed already demonstrated in a recent publication (64). Finally, due to the small size of samples of ERM 2 and 3 at baseline, stages 2 and 3 had to be pooled to enable our analyses and, thus, progression from stage 2 to 3 was not analyzed. Moreover, also due to the sample size, all types of ERM –either idiopathic or secondary– had to be taken into account for our analyses and this could have influenced analyses on risk factors.

In conclusion, we here report the results from the first epidemiologic study based on OCT detection of ERM in the general population. In our cohort of elderly subjects, the mean annual incidence rate was 9.42 per 100 eyes (95% CI, 7.36-12.05), corresponding to a cumulative five-year incidence of 37.57%. Five-year progression incidence was 6.86%. Identified risk factors for incidental ERM were cataract surgery, PVD, contralateral ERM and, more unexpectedly, decrease in choroidal thickness. Further studies in younger subjects will be necessary to confirm this last result and to provide more information that could explain the connection between choroidal thinning and ERM occurrence.

II.6 TABLES AND FIGURES

Figure 1 : OCT-based ERM classification in the ALIENOR study



Our classification of ERM based on SD-OCT findings for the ALIENOR study describes 4 stages as shown in this figure. A, Stage 0: absence of ERM. B, Stage 1: presence of a continuous hyper-reflective signal at the inner retinal surface, this signal has to be present on at least three consecutive sections. C, Stage 2: same characteristics as stage 1 with presence of retinal folds. D, Stage 3 corresponds to stage 2 associated with foveal depression alterations.

Table 1 : Characteristics of included and non-included eyes for analyses of ERM incidence and/or progression in the ALIENOR cohort

| Characteristics | Included (n=735) | Non included (n=513) | p-value |
|-----------------------------------|---------------------|-------------------------|-------------------|
| Males | 293 (39.9) | 173 (33.7) | 0.09 |
| Education level | | | |
| Elementary school without diploma | 58 (7.9) | 32 (6.2) | 0.32 |
| Short secondary school | 323 (43.9) | 243 (47.4) | ref |
| Higher level | 354 (48.2) | 238 (46.4) | 0.47 |
| Age, years | 81.3 ± 3.8 | 83.4 ± 4.6 | <0.0001 |
| Smoking | | | |
| Never | 461 (63.0) | 339 (67.0) | 0.27 |
| Current or past | 271 (37.0) | 167 (33.0) | |
| BMI, kg/m ² | 26 ± 4 | 25.2 ± 4.4 | 0.0139 |
| Diabetes | 76 (10.5) | 74 (14.7) | 0.09 |
| History of cataract surgery | 334 (45.9) | 259 (51.9) | 0.23 |
| Axial length, mm | 23.4 ± 1.3 | 23.9 ± 1.6 | 0.0002 |
| VMA or VPA | 215 (29.4) | 117 (23.9) | 0.15 |
| Laser eye treatment | 197 (27.4) | 141 (28.2) | 0.29 |

Data are presented as mean ± SD or frequency (%)

The values in bold indicates statistical significance (p<0.05)

Table 2 : Incidence and progression rates of ERM in the ALIENOR cohort

| | Age Group (year) | | p-value | Sex Group | | Total (n=735) | 5-y Risk, % | |
|---|---------------------|----------------------|---------------|---------------------|----------------------|------------------|----------------------|-------|
| | < 80 (n=325) | ≥ 80 (n=410) | | Men (n=293) | Women (n=442) | | | |
| Incidence per 100 EYs, n=378 (95% CI) | 6.76 (4.72-9.68) | 9.39 (7.36-11.98) | 0.0086 | 6.52 (4.27-9.97) | 8.72 (6.72-11.31) | 0.0293 | 9.42 (7.36-12.05) | 37.57 |
| Progression per 100 EYs, n=357 (95% CI) | 1.79 (0.92-3.48) | 1.43 (0.88-2.32) | 0.37 | 2.50 (1.39-4.52) | 1.35 (0.81-1.39) | 0.019 | 1.142 (0.88-2.30) | 6.86 |

The values in bold indicate statistical significance. (p<0.05)
EY, eye-year

Table 3 : Age and sex-adjusted associations of incident ERM with potential risk factors in the ALIENOR study

| Risk factors | Incident eyes (n=102) | Non incident eyes (n=185) | Hazard Ratio* (95% CI) | p-value |
|-------------------------------|----------------------------------|--------------------------------------|-----------------------------------|----------------|
| History of cataract surgery | 50 (49.0) | 60 (32.4) | 1.90 (1.18-3.07) | 0.0081 |
| VPA or VMA | 43 (42.2) | 57 (30.8) | 1.37 (0.86-2.18) | 0.19 |
| Prior ocular laser treatment | 26 (25.5) | 33 (17.8) | 1.44 (0.84-2.47) | 0.18 |
| Choroidal thickness, per 10µm | 195.39 ± 78.89 | 218.14 ± 83.71 | 0.96 (0.94-0.99) | 0.0118 |
| ERM in the contralateral eye | | | | |
| Stage 1 | 25 (24.5) | 34 (18.4) | 1.55 (0.94-2.56) | 0.042 |
| Stage 2 or 3 | 9 (8.8) | 8 (4.3) | 2.26 (1.06-4.81) | |
| Current or past smokers | | | | |
| <85 years old | 23 (29.1) | 38 (37.6) | 0.93 (0.51-1.71) | |
| ≥85 years old | 13 (56.5) | 21 (25.0) | 4.85 (1.95-12.07) | 0.0026 |
| BMI, per 1kg/m ² | 26.25 ± 4.41 | 26.56 ± 4.05 | 0.98 (0.93-1.03) | 0.48 |
| Diabetes | 8 (7.8) | 20 (10.8) | 0.88 (0.43-1.79) | 0.73 |
| High blood pressure | 61 (61.6) | 103 (56.0) | 1.17 (0.72-1.90) | 0.53 |
| Antihypertensive treatment | 62 (60.8) | 125 (67.6) | 0.76 (0.47-1.23) | 0.26 |

All analyses did not include eyes with missing datas. Therefore, 91 eyes were excluded.

Data are presented as mean ± SD or frequency (%)

* gender adjusted

CI, confidence interval

The values in bold indicates statistical significance p<0.05

Table 4 : Multivariate analysis for incident ERM in the ALIENOR cohort

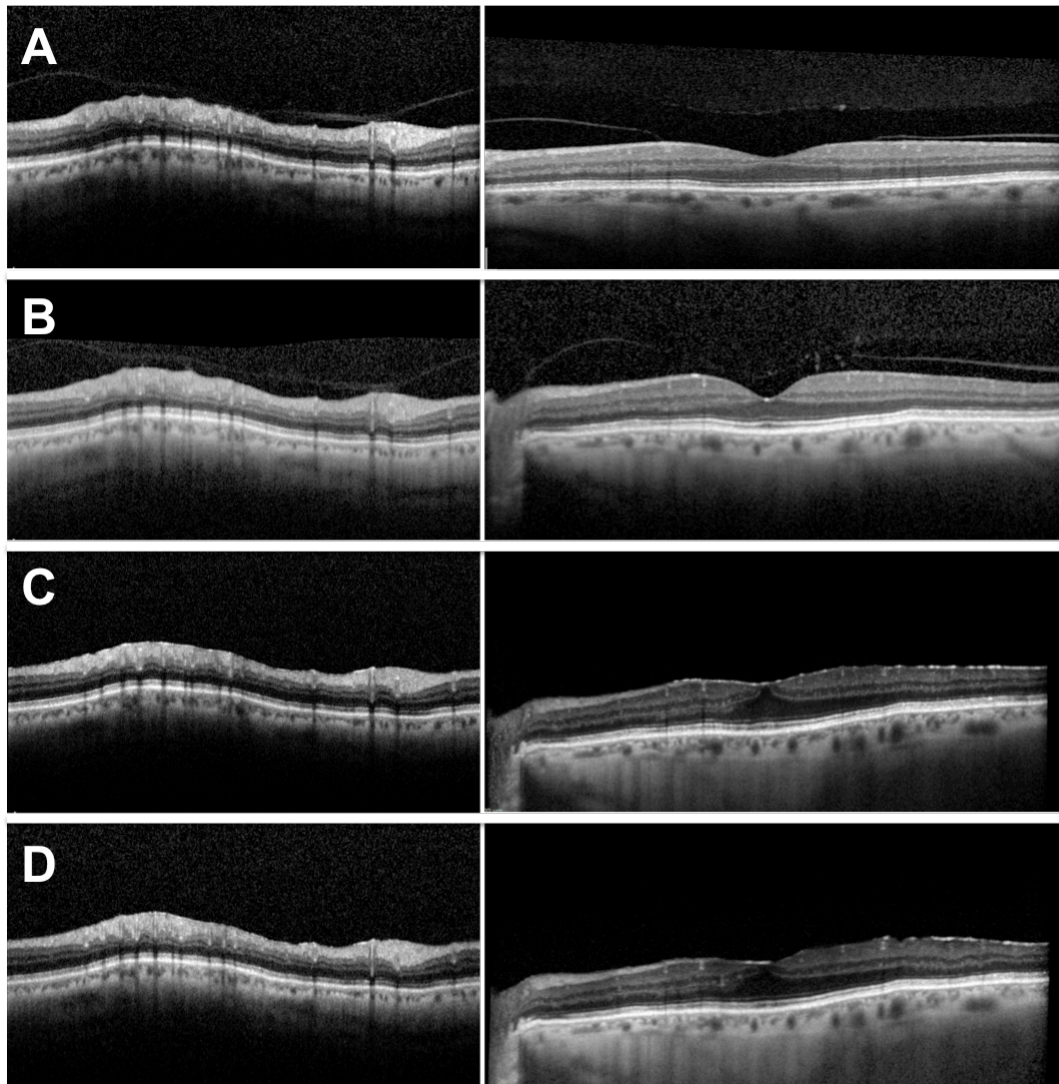
| Risk factors | Hazard Ratio* | 95% CI | p-value |
|-------------------------------|----------------------|---------------|----------------|
| History of cataract surgery | 1.86 | 1.15 ; 2.99 | 0.0108 |
| VMA or VPA | 1.64 | 1.03 ; 2.61 | 0.038 |
| Choroidal thickness, per 10µm | 0.96 | 0.94 ; 0.99 | 0.0094 |
| Current or past-smokers | | | |
| < 85 years old | 0.86 | 0.45 ; 1.64 | 0.0022 |
| ≥ 85 years old | 4.81 | 1.91 ; 12.11 | |
| Sex | 1.38 | 0.78 ; 2.44 | 0.27 |

* gender adjusted

The values in bold indicates statistical significance p<0.05

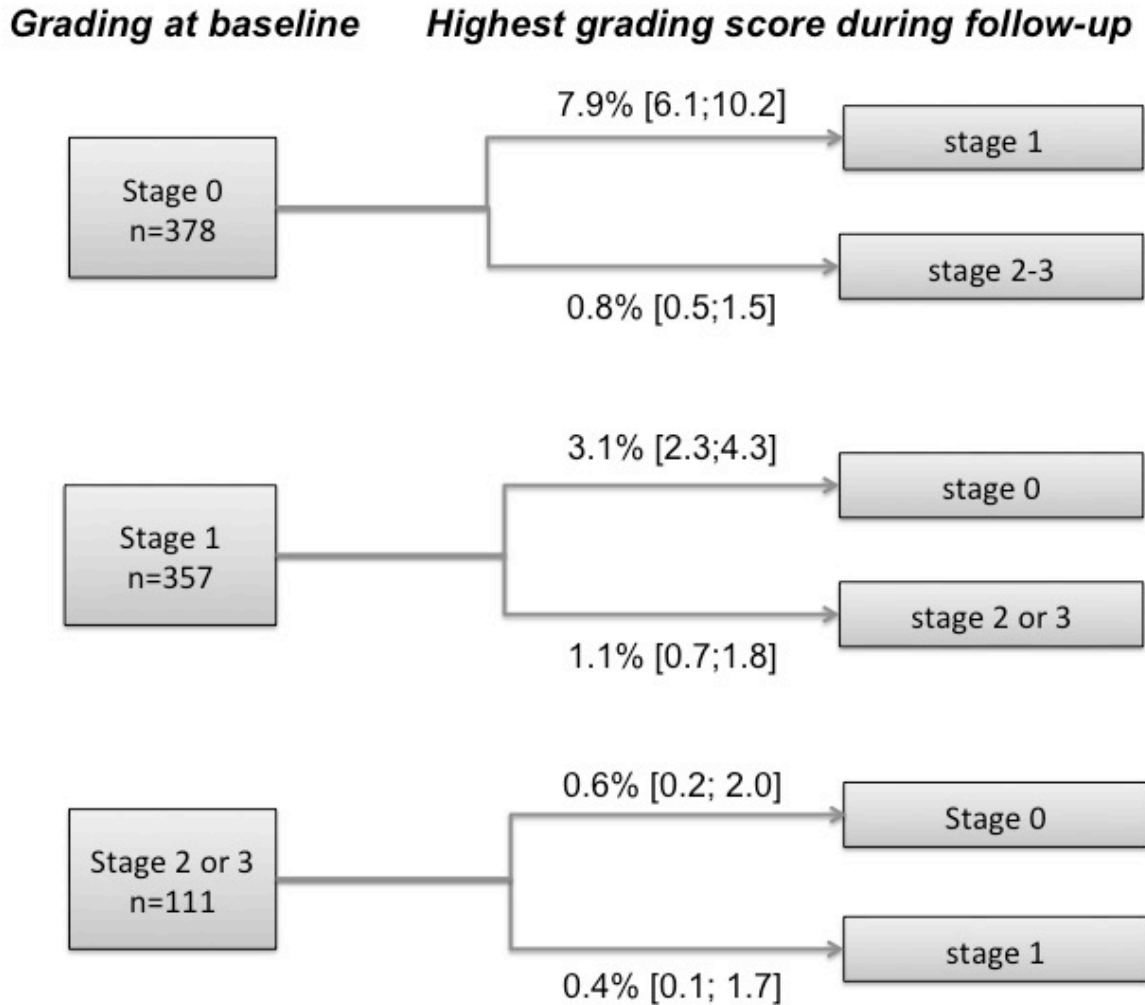
CI, confidence interval

Figure 2 : SD-OCT images of the eye of an ALIENOR participant with VPA and VMA at baseline who developed incident ERM during follow-up.



SD-OCT images of the same eye during the entire follow-up period, left images are centered on the optic nerve head and right scans on the macular area. A, SD-OCT examination at baseline shows VPA and VMA but no associated ERM (ERM stage 0). B, Same eye 2 years later (wave 2 visit): VPA is still present but posterior vitreous cortex starts its separation from the macular area, initiating posterior vitreous detachment. No ERM is observed. (C) At wave 3 visit, VPA spontaneously released and ERM stage 3 appears. (D) At wave 4 visit, SD-OCT examination remained stable.

Figure 3 : Evolution of ERM grading score for each eye during ALIENOR study



This figure illustrates the evolution of the ERM grading score from baseline through follow-up. For each analyzed eye only the highest (or lowest) variation is considered. 7.9% ERM stage 0 at baseline reached stage 1 during follow-up, only 0.8% of stage 0 reached stage 2 or 3. 1.1% of ERM stage 1 reached stage 2 or 3, while 3.1% of ERM stage 1 evolved down to ERM stage 0. Few cases of stages 2 or 3 were graded during follow-up at a lower stage.

[] 95% confidence interval

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III CONCLUSION ET PERSPECTIVES

Notre étude a permis d'établir le taux d'incidence de membranes épirétiniennes (MER) au sein d'une population générale âgée de plus de 80 ans, retrouvé à 9,42 pour cent yeux-année, soit une incidence cumulée à 5 ans de 37,7%. Cette dernière est presque 10 fois supérieure à celle retrouvée dans les études d'incidence similaires (37, 38). Cette différence peut être expliquée par l'utilisation exclusive des rétinothographies pour dépister les MER dans ces études, alors que nous nous sommes basés uniquement sur l'OCT haute définition. Celui-ci a déjà montré des capacités diagnostiques supérieures aux rétinothographies lors d'études préalables (28, 40). De plus, la majorité des cas incidents étaient des stades 1, correspondant à une hyperreflectivité pré-rétinienne présente sur au moins 3 coupes consécutives de l'OCT maculaire dans notre classification. Ce stade très précoce de MER peut facilement être indétectable sur les rétinothographies, comme le montre la **Figure 4**. Afin de confirmer la pertinence de ce stade 1 en tant que prolifération vitréoretinienne débutante, il serait intéressant de réaliser d'autres études épidémiologiques sur les MER à partir de la même classification. Une étude d'incidence et d'évolutivité sur plusieurs années, dans une population plus jeune, permettrait de confirmer nos résultats et d'analyser à nouveau l'évolution des stades 1 au cours du temps.

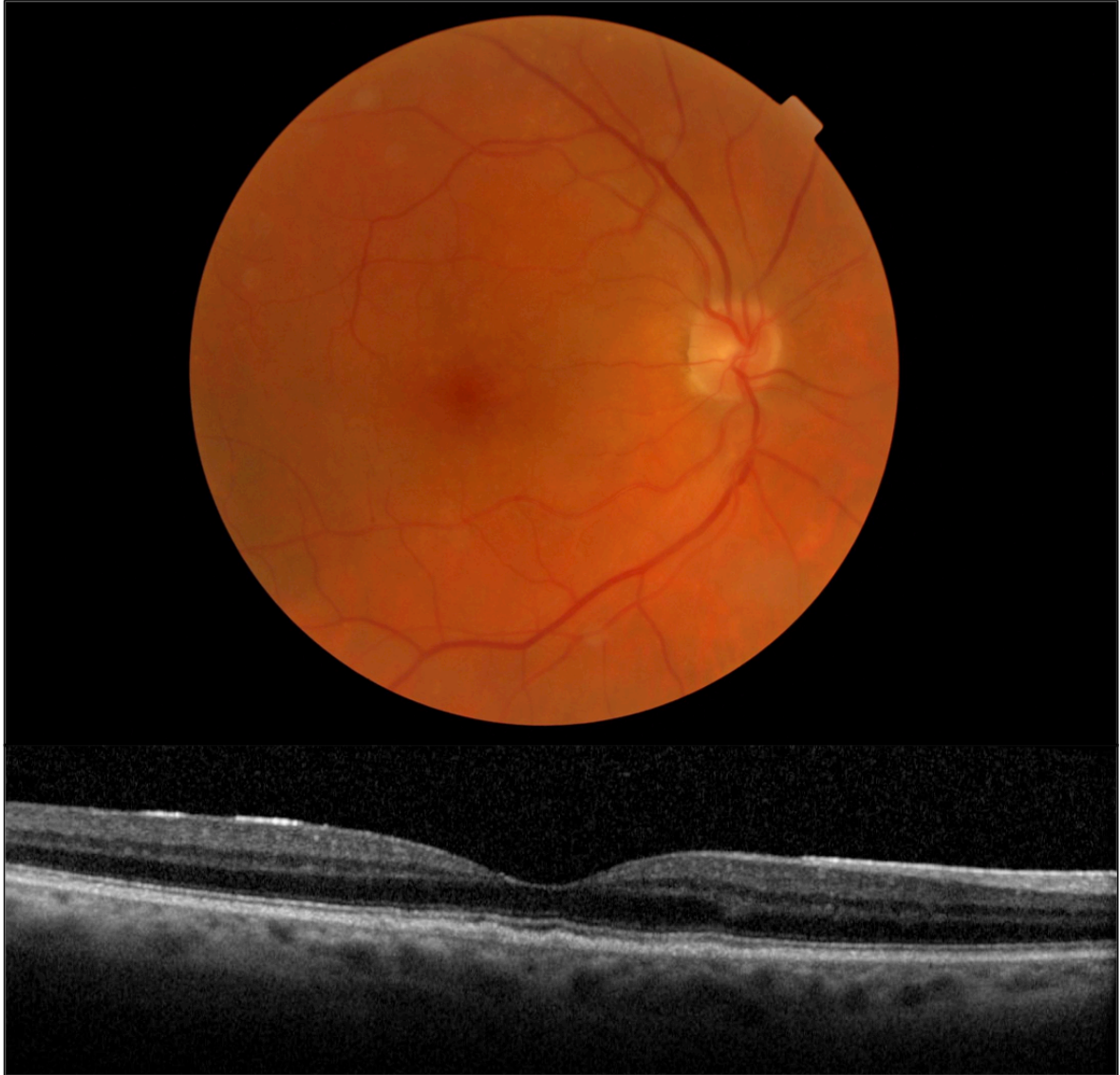
Nous avons retrouvé un taux de progression des MER (c'est à dire passant du stade 1 vers le stade 2 ou 3) relativement faible avec seulement 20 yeux sur 357 progressant, soit un taux de progression de 1,142 pour 100 yeux-année. Nous avons trop peu de cas évolutifs pour déterminer les facteurs de risques de progression, et trop peu de stades avancés pour établir le taux de progression du stade 2 vers un stade 3. Une surveillance allégée peut néanmoins être préconisée en cas de MER stade 1 chez des patients de plus de 80 ans, avec peu de risque de devenir symptomatique. Une étude similaire avec plus de cas serait à envisager afin d'identifier les facteurs de risques de progression des MER, et de pouvoir intensifier la surveillance en cas de risque de progression avéré. La vitrectomie avec pelage de la limitante interne reste toujours le traitement de référence aujourd'hui en cas de MER symptomatiques (41).

Nous avons pu montrer que l'incidence des MER est peu liée à des facteurs de risques systémiques, mais semble être associée à certains facteurs locaux comme la chirurgie de la

cataracte, l'adhésion vitréopapillaire ou vitréomaculaire. En 2001, Jahn C.E *et al.* étudiaient la prévalence des MER à 15 jours, 6 mois puis 9 mois d'une chirurgie de la cataracte, à partir de l'examen du fond d'œil. Ils retrouvaient alors une augmentation de la prévalence des MER de 71.4% pendant les 6 premiers mois, avec une majorité de stades précoces (« cellophane macular reflex ») (42). Il pourrait être intéressant de réaliser le même type d'étude clinique, en diagnostiquant les MER à partir de l'OCT uniquement, afin de mettre en application notre classification. Nous pourrions observer l'évolution de la prévalence post opératoire et déterminer quels stades de MER prédominent.

Enfin, pour la première fois, l'épaisseur choroïdienne a été retrouvée comme facteur protecteur vis à vis de l'incidence des MER dans notre étude. Cette association reste à éclaircir. Une étude Coréenne récente a étudié la densité vasculaire choroïdienne sur l'OCT en face, retrouvant une association significativement positive entre la densité vasculaire choroïdienne et l'épaisseur choroïdienne (43). Par déduction, une augmentation de la vascularisation choroïdienne protégerait de la formation des MER. Ces résultats vont dans le même sens que ceux de Yu.Y *et al.*, qui retrouvent une perfusion choriocapillaire significativement diminuée sur l'OCT angiographie des patients atteints de MER comparativement aux yeux sains controlatéraux (44). Le débit sanguin choroïdien permet l'apport d'oxygène et de nutriments nécessaires au bon métabolisme rétinien, surtout au niveau fovéolaire où celui ci est exclusif (45). Selon notre étude, il pourrait aussi influencer les mécanismes à l'origine de la prolifération cellulaire vitréoretinienne. Ces résultats restent bien sûr à confirmer par d'autres études spécifiques.

Figure 4 : Membrane épiretinienne stade 1 d'un participant de l'étude ALIENOR avec rétino­photographie correspondante



En bas de l'image, l'OCT d'un participant de l'étude ALIENOR au stade 1 de la classification des MER. En haut, la rétino­photographie correspondante, sans anomalies décelables.

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SERMENT D'HIPPOCRATE

Au moment d'être admise à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels 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 leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des 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 les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admise dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçue 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. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui 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 déshonorée et méprisée si j'y manque.

INCIDENCE, PROGRESSION AND RISK FACTORS FOR EPIRETINAL MEMBRANES IN THE ELDERLY : THE ALIENOR STUDY

Purpose: To determine the incidence, progression rate and risk factors for epiretinal membranes (ERMs) in a population of French elderly subjects.

Methods: 735 eyes of 413 participants of the ALIENOR study were included between 2009 and 2010. Participants were reevaluated every two-years between 2009 and 2017 (corresponding to 3 follow-up visits). All included eyes had gradable spectral-domain optical coherence tomography (SD-OCT), retinal images at baseline and at least one follow-up data collection point. A classification of ERMs using SD-OCT findings was set up to evaluate ERM incidence and progression.

Results: The incidence rate of ERM was 9.42 per 100 eye-years (95% confidence interval (CI), 7.36-12.05) in our population, corresponding to a five-year cumulative incidence of 37.57%. ERM incidence was significantly associated with smoking after 85 years (Hazard Ratio (HR), 4.81; $p=0.022$), cataract surgery (HR, 1.86; $p=0.0108$), presence of vitreomacular or vitreopapillary adhesion (HR, 1.64; $p=0.038$) and decrease in choroidal thickness (HR 1.04; $p=0.0094$). The five-year cumulative progression rate was 6.86%.

Conclusion: Due to the systematic use of SD-OCT images, early ERMs were found to be far more frequent in our population than previously described. Incident ERMs were associated with three main ocular risk factors: cataract surgery, vitreous adhesion and interestingly, choroidal thickness.

Key words: cumulative incidence, epidemiologic study, elderly subjects, epiretinal membrane, eye aging, incidence rate, general population, population-based study, progression rate, risk factors

Discipline: Ophtalmology

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