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Clinical Characteristics and Risk Factors of Extensive Macular Atrophy with Pseudodrusen

The EMAP Case-Control National Clinical Trial

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Purpose: To assess the association of clinical and biological factors with extensive macular atrophy with pseudodrusen (EMAP) characterized by bilateral macular atrophy occurring in patients aged 50 to 60 years and a rapid progression to legal blindness within 5 to 10 years.

Design: A national matched case-control study.

Participants: Participants were recruited in 10 French Departments of Ophthalmology and their associated clinical investigation centers. All 115 patients with EMAP had symptoms before the age of 55 years due to bilateral extensive macular atrophy with a larger vertical axis and diffuse pseudodrusen. Three controls without age-related macular degeneration (AMD) or retinal disease at fundus examination were matched for each patient with EMAP by gender, age, and geographic area (in total 415).

Methods: Subjects and controls underwent an eye examination including color, red-free autofluorescent fundus photographs and spectral-domain optical coherence tomography with macular analysis. The interviews collected demographic, lifestyle, family and personal medical history, medications, and biological data. Associations of risk factors were estimated using conditional logistic regression.

Main Outcome Measures: Extensive macular atrophy with pseudodrusen status (cases vs. controls).

Results: Extensive macular atrophy with pseudodrusen most frequently affected women (70 women, 45 men). After multivariate adjustment, family history of glaucoma or AMD was strongly associated with EMAP (odds ratio [OR], 2.3, $P = 0.008$ and OR, 1.5, $P = 0.01$, respectively). No association was found with cardiac diseases or their risk factors. Mild and moderate kidney disease and higher neutrophil rate were associated with a reduced risk of EMAP (OR, 0.58, $P = 0.04$; OR, 0.34, $P = 0.01$; and OR, 0.59, $P = 0.003$, respectively). On the contrary, eosinophilia (OR, 1.6; $P = 0.0002$), lymphocytosis (OR, 1.84; $P = 0.0002$), increased erythrocyte sedimentation rate (OR, 6.5; $P = 0.0005$), decreased CH50 ($P = 0.001$), and high plasma C3 level ($P = 0.023$) were significantly associated with a higher risk of EMAP.

Conclusions: This study documents an association between EMAP and family history of AMD and glaucoma, a clear female predominance, and a systemic inflammatory profile. The reduced CH50 and increased C3 plasma values could reflect a more severe complement pathway dysfunction than in AMD, leading to early pseudodrusen and rapid development of geographic atrophy. There is no association of EMAP with AMD cardiac diseases or cardiac risks, including cigarette smoking. *Ophthalmology 2016;123:1865-1873 © 2016 by the American Academy of Ophthalmology.*

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Extensive macular atrophy with pseudodrusen (EMAP) affects patients at approximately age 55 years.[1] It is defined as a retinal dystrophy characterized by a simultaneous and symmetric extensive macular atrophy with a striking larger vertical axis along involving the posterior pole and the fovea (Figs 1–3). Macular lesions always are surrounded by numerous and widespread pseudodrusen. Paving stone lesions can be associated in the far peripheral retina. In regard to the symptoms, progressive night blindness is followed by a rapid, bilateral, and central visual decrease. Within 3 to 10 years, patients with EMAP become legally blind. Despite similar atrophic and pseudodrusen lesions, EMAP is distinct from atrophic age-related macular degeneration (AMD) because it begins earlier (age 50–55 years), affects both eyes at the same time, and destroys the central vision in only a few years.

Age-related macular degeneration remains the leading cause of severe impairment of visual function in people aged more than 50 years in industrialized countries. The atrophic form of AMD is one of the late forms, observed in older patients (mean age of onset of atrophic stage, 78 years), with an estimated prevalence of 0.16% at age 60 years and 11.3% at age 90 years.[2] The natural history of atrophic AMD is different from EMAP because it begins with small, rounded atrophic spots that slowly progress toward confluence, with a long period of foveal sparing.[3–8] In addition, macular lesions are unilateral, with 1 eye affected during several years. Atrophic AMD was classified recently into several phenotypic subtypes according to the autofluorescence pattern.[9] One subgroup, the diffuse trickling geographic atrophy (DTGA), is characterized by high-speed progression (3.2 mm^2/year) of the atrophy (Figs 1–3). Pseudodrusen are constant lesions in DTGA.[10] In addition, DTGA frequently is bilateral (70% of cases), and foveolar involvement (42%) may be noted early.[11] Late AMD, including geographic and neovascular forms, is associated with advanced age, smoking, fat intake, obesity, AMD family history, and genetic susceptibility.[12–21]

Pseudodrusen-like deposits are part of the phenotypic characteristics of EMAP. Pseudodrusen encountered in 10% to 90% of patients with AMD are associated with late atrophic AMD and choroidal neovascularization.[22–28] They appear as interlacing yellowish lesions enhanced by blue light in the superior outer macula and may extend in the other quadrants and the periphery. In spectral-domain optical coherence tomography, they are not beneath the retinal pigment epithelium (RPE) like classic AMD drusen, but in the subretinal space at the level of the RPE or in between the RPE and the photoreceptors and appearing as nodular or less frequently diffuse lesions (Fig 3). In EMAP, pseudodrusen-like deposits are not restricted to the posterior pole, affect the entire mid-peripheral retina, appear as subretinal deposits, and are not associated with any other type of drusen. In AMD, pseudodrusen are associated with advanced age (>80 years), female gender, cardiac diseases, and AMD family history.[22–24,26,28–32]

To date, EMAP pathophysiology and risk factors remain unknown. Extensive macular atrophy with pseudodrusen could be a distinct clinical entity caused by a specific pathogenic mechanism. We carried out a large epidemiologic and environmental national case-control study to assess the associations of EMAP with clinical and biological factors.

Methods

Study Design

This case-control study included patients with EMAP and controls between May 2011 and July 2014. Three controls were matched to each case on age (±5 years), sex, and residential area (4 French areas: North, South, East, and West). Ten French centers specializing in retinal diseases participated in the recruitment of patients with EMAP (Créteil, Lille, Lyon, Marseille, Montpellier, Nantes, Paris [3 centers], and Reims). Clinical research centers of 4 French cities selected according to their geographic situation (Montpellier in the south of France, Lille in the north, Tours in the west, and Dijon for the east) enrolled the controls. Control subjects were recruited through volunteer databases and calls for volunteers in the media. This research followed the tenets of the Declaration of Helsinki. Participants gave written consent for their participation in the study. The design of this study was approved by the local ethical committee (CPP Sud Méditerrannée IV, decision March 8, 2011).

Population

Common inclusion criteria for cases and controls were (1) women and men aged 40 to 80 years and (2) European origins.

Cases

Inclusion criteria for the patients with EMAP were (1) onset of functional signs before the age of 55 years, (2) macular patch of atrophy with a larger vertical diameter, and (3) diffuse peripheral pseudodrusen. For each patient, age at examination, refraction, and visual acuity were noted. The best-corrected visual acuity was obtained with Snellen charts. Reading visual acuity was assessed with the current French near-vision chart (Parinaud). Color fundus frames were performed with the Topcon Imagenet (Ophthalmic Imaging Systems, Tokyo, Japan) or the Nidek AFC 330 nonmydriatic automated fundus camera (Nidek Inc., Tokyo, Japan). Autofluorescence imaging and spectral-domain optical coherence tomography were performed with the Combined Heidelberg Retina Angiograph + OCT Spectralis device (Heidelberg Engineering, Dossenheim, Germany). When the 2 national coordinators (CH and IM) disagreed on clinical features, the patient was not included.

Controls

Color fundus frames were systematically performed with a nonmydriatic device (Nidek AFC 330 nonmydriatic automated fundus camera; Nidek Inc.) to exclude subjects with any retinal disease or atrophic macular lesions. Controls older than 70 years of age with uncomplicated drusen could be included.

Clinical and Lifestyle Risk Factors

For both cases and controls, a medical questionnaire on personal and family medical history was completed during a face-to-face interview with the ophthalmologist or clinician. Family history focused on AMD, glaucoma, Alzheimer disease, and personal history on hypertension, diabetes, hypercholesterolemia, cardiac diseases, and strokes. Anthropometric measurements (height and weight) and systolic and diastolic blood pressures were