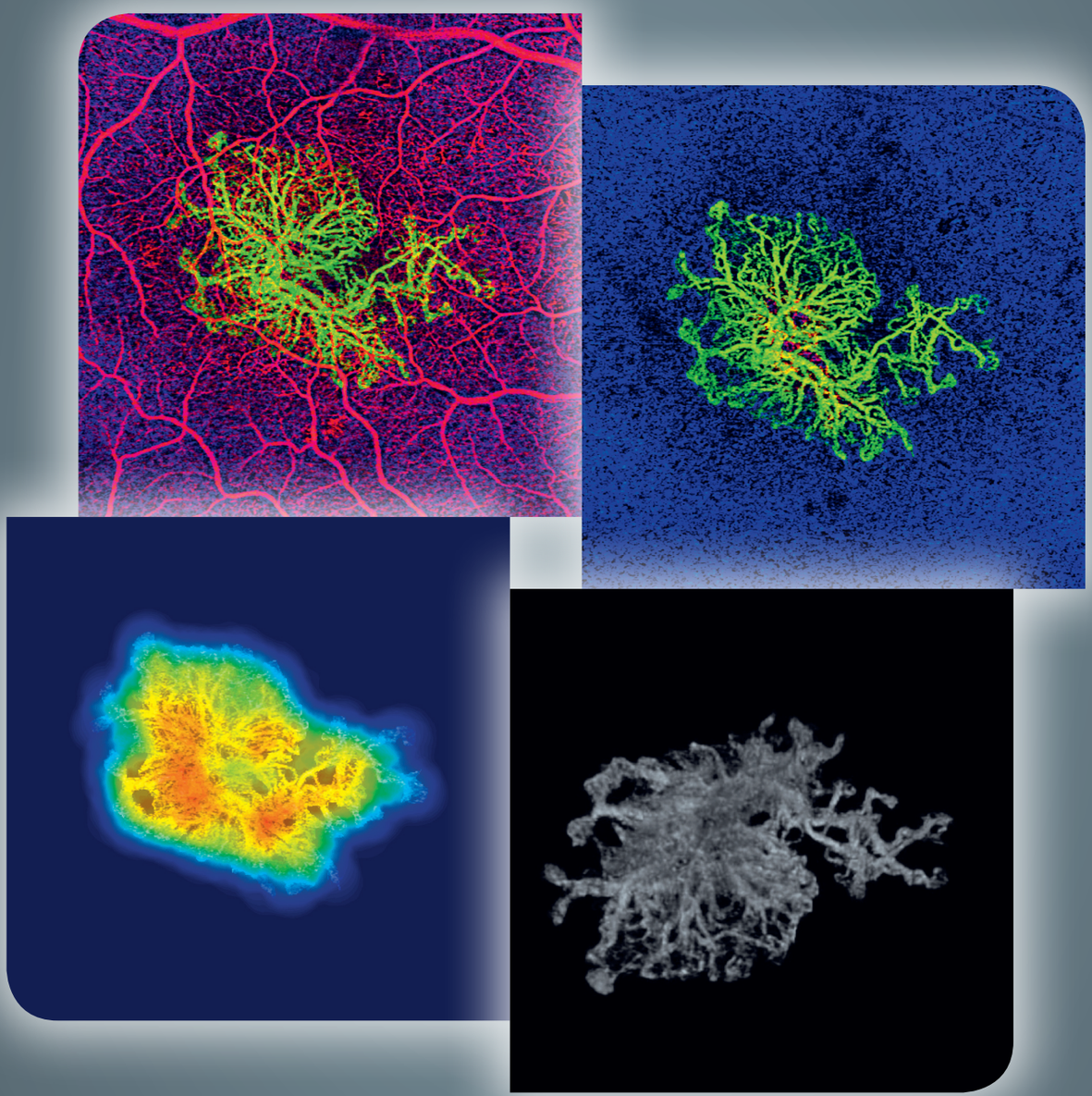
AMD
AN OVERVIEW OF CLINICAL FORMS



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Théa
let's open our eyes

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Age-related macular degeneration: epidemiology, environmental and genetic risk factors

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Age-related macular degeneration (AMD) is a common eye disease among older people, causing a severe visual impairment. The pathophysiology of AMD remains largely unknown: it is a complex, multi-factorial disease involving aging of the retina and a combination of environmental and genetic factors.

1. Epidemiology

The majority of the large epidemiological studies on age-related macular degeneration (AMD) have been conducted in the United States[1-3]. The Beaver Dam Eye Study[3] estimated the prevalence of advanced forms of the disease at 1.6% of the general population and 7.1% in people over 75 years old. In Europe, the data from the EUREYE Study[4] are consistent with the American data and indicate a prevalence of 1.2% for geographic atrophy and 2.3% for exudative forms. In France, the disease affects an estimated 1.5 million people[4]. It is estimated that by 2020, around 196 million people worldwide will be suffering from a form of AMD[5].

2. Constitutional and environmental risk factors

1) Constitutional factors

Several constitutional factors have been studied in order to identify their role in the onset of the disease. Age is obviously a factor, with prevalence increasing with age. In addition, the prevalence of the disease varies depending on the ethnic origin of the studied populations[6]. Advanced forms of AMD are more common in Caucasian populations than in dark-skinned populations[7]. In terms of sex, some meta-analyses have not found any differences in disease prevalence between men and women[7]. However, the Beaver Dam Study[3] found a higher incidence of age-related maculopathy in women over 75 compared to men of the same age.

Multiple studies have established correlations between certain cardiovascular risk factors and AMD. Klein *et al.*[8] found a correlation between patients with neovascular AMD and the presence of cardiovascular disease. Data from the AREDS study reveal increased cardiovascular mortality among patients with AMD[9]. However, other studies, such as AREDS Report No. 19, have not found any correlation between AMD and angina pectoris[10]. High blood pressure has been studied independently. The results are similarly divergent, with some studies finding an association[11] and others finding none[12].

Blood lipid level has also been considered independently in multiple studies. Lipid metabolism has been shown to be involved in the physiopathology of AMD, particularly via the role of apolipoprotein E, which has been suggested as a genetic susceptibility factor for AMD[13,14]. Here again, the results are contradictory when it comes to establishing a correlation between blood lipids and disease susceptibility.

2) Environmental factors

a) Smoking, alcohol, body mass index (BMI)

Smoking is the main identified environmental risk factor[15]. Alcohol consumption has also been reported as a major risk factor for age-related maculopathy (ARM)[16]. A more recent study found an increased incidence of atrophic AMD at 15 years with excessive alcohol consumption[17]. BMI is also a proven risk factor for AMD[18].

b) Omega-3 and vitamins

Omega-3s play a physiological role in the photoreceptor outer segments. Long-chain polyunsaturated fatty acids (DHA: docosahexaenoic acid and EPA: eicosapentaenoic acid) are synthesised from linoleic acid in food. A meta-analysis of omega-3 consumption found that it was associated with a reduced risk of developing AMD[19].

Lutein and zeaxanthin are the two beta-carotenes found in the retina, with maximum concentration in the macula. These pigments absorb at least 40% of blue light. Several studies have found that consuming lutein and zeaxanthin is beneficial in warding off the disease[20], but these results are contradicted by other studies[3,21].

Antioxidants have also been studied. AREDS Report No. 8[22] established a significant association between antioxidant (vitamins C and E and beta-carotene) and zinc intake and a reduced risk of exudative AMD, compared to placebo.

The NAT 2 study attempted to evaluate the efficacy of DHA and EPA supplementation in the prevention of choroidal neovascularization at three years in patients with age-related maculopathy (ARM)[23]. This study found a significant reduction (68%) in the risk of developing an exudative form of the disease in patients with the highest level of DHA and EPA. Genetic analysis of this cohort also demonstrated that the protective effect of the supplementation was maximum in patients who did not have the C-allele of the CFH Y402H polymorphism[24].

3. Genetic risk factors for AMD susceptibility and genetic factors impacting treatment response

Our understanding of the genetic factors behind AMD has developed alongside advances in genetic analysis methods, ranging from family-based analysis to association studies of large populations with AMD compared to control populations.

1) Genetics in family cases

Genetic susceptibility to early, intermediate and advanced AMD was first hypothesised by Gass in 1973[25]. Gass had observed several families with cases of AMD and hypothesised that the disease was an autosomal dominant disorder. Other studies of family aggregation have identified a higher frequency of the disease in the relatives of existing patients[26-28].

The existence of a genetic component has also been suggested in light of the high phenotypic concordance between monozygotic twins[29-31]. Monozygotic twin studies can also be used to assess the “heritability” of a disease, i.e. the proportion of the phenotype attributable to the genotype. The heritability of AMD is estimated to be between 45% and 70%, based on the studies conducted[32,33].

Genetic linkage studies conducted in the families of people suffering from the disease have identified various chromosomal loci of susceptibility. In 1998, Klein *et al.*[34] published the first linkage study, which mapped a locus of susceptibility to *1q*. Several years later, this locus was found to contain one of the major genes for susceptibility: *CFH*[35].

All of these family-based studies have clear limitations due to certain characteristics of AMD. The advanced age of patients makes it harder to find families for analysis, and non-Mendelian inheritance makes the disease difficult to analyse in a limited number of patients. Researchers therefore changed tack and began comparing populations with AMD to control populations, in order to study the distribution of genetic susceptibility markers.

2) Population genetics in AMD

a) Candidate gene approach

Certain genes, known as "candidate genes”, can be selected for analysis to determine their involvement in the physiology of a disease. For example, the lipid composition of soft drusen led researchers to study the genes involved in lipid metabolism, revealing an association with the 4 allele of the *apolipoprotein E* gene, which was found to play a protective role[36].

Candidate genes can also be genes already known to be involved in other types of retinal dystrophy or Mendelian-inherited maculopathy, such as the *ABCA4* gene, which is involved in Stargardt disease[37]; the *VDM2/BEST1* genes, involved in Best disease[38]; and the *RDS* gene, involved in numerous hereditary forms of retinal dystrophy[39].

These genes can also be identified by sequencing candidate regions highlighted in segregation studies or through positional cloning. The *HTRA1/ARMS2* region has been identified using this approach.

b) Genome-wide associations studies

More recently, genome-wide association studies (GWAS) and studies of candidate regions have enabled researchers to identify numerous other predisposing or protective variants involved in disease susceptibility. This approach has confirmed the results in the literature, as well as identifying new pathways potentially involved in the physiopathology of AMD. The most recent *GWAS*[40], published in 2015, summarises the full extent of our understanding of this field, identifying 52 variants associated with increased susceptibility to the disease in 34 loci.

c) Other types of variants causing susceptibility to AMD

Improvements in sequencing techniques have enabled researchers to study genetic variations other than single-nucleotide polymorphisms[41]. For example, chromosomal rearrangement, alternative splicing of certain isoforms, copy number variation (CNV), micro-ribonucleic acids (miRNA) and other non-coding RNAs, and epigenetics can all be investigated as potential factors involved in AMD susceptibility and physiopathology. Insertions and deletions in the *CFH* locus[42-44] have been identified in several studies, alongside CNVs in the same region[45,46]. Non-coding microRNAs have been implicated in the physiopathology of exudative AMD due to their supposed role in the regulation of both angiogenesis and inflammation[47]. Epigenetics also appears to play a role, with DNA methylation implicated in the onset of the disease[48].

3) Impact of genetics on treatment response

In terms of the severity of the disease, genotype-phenotype correlation studies have found an association with the single-nucleotide polymorphism rs10490924 in *ARMS2/HTRA1* in patients with advanced bilateral forms of AMD[49], as well as severe and early forms[50]. rs1061170 in *CFH*[51] is another polymorphism associated with bilateral forms. Additionally, a recent study identified a correlation between a polymorphism in C3 and large vascularised pigment epithelial detachments[52].

In terms of response to anti-VEGF treatment, several single-nucleotide polymorphisms in the *VEGF* A gene have been found to correlate with a better treatment response[53-56], as have certain polymorphisms in the gene coding for the *VEGF-R2* receptor [57]. Single-nucleotide polymorphisms in the *CFH*, *ARMS2* and *HTRA1* genes—which all play a key role in AMD—have also all been found to correlate with a better response to anti-VEGF treatment[58-61]. For each of these variants, some of the published studies did not find any association with treatment response[62].