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Age related macular degeneration

Is our current clinical classification of AMD up to the job?

G Malek, S W Cousins

Various combinations of risk factors and mechanisms may explain the complexity observed in AMD patients

Age related macular degeneration (AMD) is a "heterogeneous group of disorders" resulting in severe vision loss. The heterogeneity is a reflection of the variability of symptoms, clinical findings, and natural history observed in patients as well as the fact that AMD affects many cell types in the eye, including the neural retina, photoreceptors, retinal pigment epithelium (RPE), Bruch's membrane, and the choriocapillaris. Clinically, "dry" or early AMD is characterised by large drusen and RPE pigmentary changes that can progress to an advanced stage, geographic atrophy. "Wet" or neovascular AMD, another manifestation of advanced disease, is characterised by choroidal neovascularisation (CNV). Clinical classification of early AMD is based on photographic assessment of drusen size and extent in the macula.[1] These classification systems are also used by investigators interested in the analysis of genetic, epidemiological, and morphological features of AMD.

The pathological hallmark of early AMD is the accumulation of lipid and protein rich deposits (drusen and basal deposits) between the RPE cells and the choroid. The pathogenic mechanisms of deposit formation in AMD are still emerging, but the best data indicate involvement of lipid biochemistry, oxidative stress, dysregulated extracellular matrix molecules, and inflammation. Not surprisingly, diversity has also been observed in epidemiological associations between environmental and genetic risk factors for AMD, many of which vary among ethnicities. With this in mind, it follows, that various combinations of risk factors and mechanisms may explain the complexity observed in AMD patients, giving rise to a "heterogeneous group of disorders." But, is our current classification system comprehensive enough to allow us to tease out the complex interrelations between genetics and environment?

HOW DO WE ASSESS THE CONTRIBUTION OF GENETICS VERSUS ENVIRONMENT?

One way is to identify environmental, genetic, and systemic health differences that are involved in the development of AMD across cultures and ethnicities. These studies would provide a new understanding of the dynamic interplay between genes and environment. A significant breakthrough in the search for genetic contributors in AMD came in the spring of 2005, when four independent groups across the United States, published their findings identifying a DNA sequence variant in complement factor H that is associated with AMD. They reported that this variant, a non-synonymous or disease relevant Single nucleotide polymorphism (SNP) corresponding to a tyrosine to histidine polymorphism at position 402 (protein: Y402H, cDNA: T1277C), significantly increases the odds for developing AMD to as high as 7.4. So far, identification of an association this significant had been unprecedented in the AMD field. Since then several additional studies have confirmed these findings.[2 3] However, the sample groups studied were white, leading to the inevitable question of what is the association of these SNP findings in other ethnic groups with or without AMD? Since the original studies, researchers have examined the risk association of Factor H in the Japanese, Icelandic,[4] and French populations.[5] With the exception of the Japanese cohort, the studies confirmed a risk association similar to that seen in white groups.[6 7] These results jointly suggest ethnic differences in AMD phenotypes, especially since drusen are less frequently observed in Japanese patients[8] and photodynamic therapy for exudative AMD is more effective in Japanese than in white people.[7] In this issue of *BJO* (p 1142) Simonelli *et al* report that the Y402H variation in the factor H gene dramatically increases the likelihood of developing AMD in the Italian population.[9] The scientists demonstrate that the risk association applies to the Italian cohort, though the odds ratio of 3.9 is lower than those reported for the French (6.93) and the US white (7.4 or 5.93) AMD patients. Clearly population differences can and do exist among groups of different European origin. These studies provide further evidence that relative inputs of genetics and environment to a disease state can vary across cultures.

The overall prevalence of dry and wet AMD and the association of risk factors are reportedly different in diverse ethnic groups. In fact the distribution of AMD has been studied in many ethnic groups including Finnish, Icelandic, New Zealanders, Australians, Italians, Hispanics, and Caribbean black patients. The rates of dry and wet AMD in these groups are different, as are the relation between AMD and common risk factors. For example, the prevalence of AMD and specifically drusen and RPE changes among black people are purportedly lower than in white people, while the rates of wet AMD among the two groups are

similar.[10] Additionally, in the Latino community, co-factors such as smoking and heavy alcohol consumption, particularly beer, are associated with a greater risk of having advanced AMD.[11] While smoking is a similar modifiable risk factor in non-Hispanic white patients, the relation between alcohol consumption and AMD in white people has not been consistently shown. Collectively, these studies suggest that common pathogenic mechanisms may be associated with AMD in people of different ethnicities. But differences are clearly present, and many factors should be taken into account when studying and classifying AMD.

HOW MIGHT BETTER CLASSIFICATION OF THE DISEASE IMPROVE KNOWLEDGE LEARNED FROM AMD RESEARCH?

Currently the diagnosis of AMD is defined by the clinical detection of drusen in the macula. Is this the best case definition for epidemiological and genetic studies? Postmortem tissue analysis of AMD eyes has revealed extreme complexity of subtypes of basal deposits and drusen. Significant variability is apparent in the thickness, location, extent, and morphological components of deposits, giving rise to controversies in the pathological classification of AMD. Fundus examination cannot distinguish between different types of deposits. What is identified clinically as a druse may actually be a thick basal deposit upon histological observation. By morphological criteria, AMD is a diffuse retinal disease and deposits are often present in the periphery. Should we be taking peripheral findings into account? For example, in a recent investigation examining the phenotypes of AMD patients with the Y402H variant of complement factor H, of 46 phenotypic features of AMD, peripheral reticular pigmentary changes were found to demonstrate the highest association with this polymorphism (Eric Postel, personal communication). Is peripheral reticular degeneration an indication of more severe AMD? These changes are not detectable by standard fundus photography. Furthermore, the molecular composition and relative distribution of lipids and proteins in drusen vary, and photography cannot yet image these biochemical differences. Similar complexity is evident for neovascular AMD. Morphological studies on CNV membranes demonstrate variable contribution of inflammatory, vascular, and fibrotic components not addressed in the clinical classification. One issue not well addressed is how phenotypic and clinical features vary among ethnicities, an issue with huge impact on the interpretation of genetic studies.

Even now, and in spite of their limitations, certain ancillary imaging and physiological testing might enhance the information learned from epidemiological and genetic studies. Several examples might include the following. Indocyanine green angiography can indirectly assess the lipid content of drusen.[12] Optical coherent tomography (OCT) can be used to assess retinal thickness, fluid accumulation, and deposit thickness. In the near future, with use of adaptive optics, high resolution hardware, and spectral domain analysis OCT will permit even more accurate and quantitative analysis of the retina and sub-RPE deposits in patients. Wide field fundus imaging with scanning laser ophthalmoscopy can now document peripheral retinal findings. Fundus autofluorescence can identify some patients at risk of progression, especially those with geographic atrophy. In the near future, two photon excited autofluorescence imaging of RPE cells will improve both morphological and spectral characteristics of the human RPE cells.[13] Resonance Raman spectroscopy of macular carotenoid pigments including lutein and zeaxanthin could prove useful in the early detection of individuals at risk for visual loss from AMD.[14] Physiological tests of photoreceptor function may be informative since rod loss with abnormal dark adaptation occurs early in the course of many AMD patients, even before the appearance of drusen.[15]

HOW MIGHT BETTER CLASSIFICATION IMPROVE CARE OF AMD PATIENTS?

One goal of AMD research should be to develop a personalised approach to individual patients. Improved predictive testing is required to stratify subsets of patients into better or worse natural prognosis, perhaps useful for identifying those who should be enrolled into prevention trials. Another potential area for future investigation is the use of blood based biomarkers. Can blood measurement of markers for inflammation, environmental toxicants, micronutrients, or other AMD associated molecules teach us about individual risk? Stratification of patients into subgroups will lead to more efficient, targeted treatments customised to the patients' specific subtype. One example is already relevant: which patient requires monthly versus quarterly anti-VEGF (vascular endothelial growth factor) therapy for their neovascular AMD? Therapeutic and diagnostic stratification can be accomplished if a new classification system incorporates information on the heterogeneity of pathology and clinical manifestations. The impact of newly discovered environmental and genetic risk factors for AMD, such as complement factor H will be realised when AMD is no longer just a ''heterogeneous group of disorders'' lumped together, but when the disorder can be carefully and meticulously subclassified on the basis of both phenotype and genotype.

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