Commentary

Terminology of sub-RPE deposits: do we all speak the same language?

So called hyaline excrescences on the lamina vitrea (or Bruch's membrane) have been a matter of debate for almost 150 years now. In 1877, Meyer speculates in *Graefes Archiv*¹ that "the very first beginning of drusen lies within Bruch's membrane and is due to tiny refractive nodules or droplets excreted by the RPE". He considered drusen as being associated not only with age, but also with inflammation and tumours and with the state of nutrition of the retina. It is amazing how little additional fundamental information concerning pathogenesis and evolution is available more than 100 years later.

Today, there is little doubt that sub-RPE (retinal pigment epithelium) deposits are somehow involved in the pathogenesis of age related macular degeneration (ARMD). However, the classical term "druse" is used by clinicians and histopathologists to describe a variety of excrescences on Bruch's membrane that differ morphologically as well as biochemically and ophthalmoscopically. The more the information has been added to this subject, the more confusing the terminology has become.

There are three major methods of classifying extracellular sub-RPE material. Ophthalmoscopically one evaluates not only the clinical picture, but also the patient's age, any family history, and additional investigations such as angiography with fluorescein or indocyanine green. Histopathologically, the tissue abnormalities are evaluated by conventional light or electron microscopy, and, thirdly, deposits can be investigated by various immunohistochemical or biochemical techniques. The common aim, of course, is to correlate all these findings in order to help our understanding of the development of ARMD and, thereby, to find better and earlier treatment modalities compared with the symptomatic treatment that is currently available. Unless, however, the same terminology is used to compare and correlate data, any analysis will only describe a very small aspect of a complex disorder and is likely to cause confusion rather than help to find a solution to the problem.

One of the most important criteria in classifying these deposits is, of course, related to their significance in neovascular membrane formation.

A clinicofundusoscopic classification of sub-RPE deposits has been given by Bressler *et al* in 1994² and by the International ARM Epidemiological Study Group in 1995,³ and large drusen and focal hyperpigmentation have been shown to be a serious clinical risk factor.⁴ Pauleikhoff and others^{5,6} have tried to correlate certain biochemical features such as lipid content and composition with *in vitro* fluorescein uptake. Other biochemical investigations revealed further components of sub-RPE deposits such as laminin, fibronectin, and glycoproteins.⁷⁻⁹ Using immunohistochemistry, the presence of ubiquitin, which is the key protein for ATP dependent proteolysis and a member of the stress protein family, has recently been demonstrated.¹⁰

Bearing in mind that the clinical description of sub-RPE deposits is limited compared with histopathology, how can we still correlate patient data and immunohistochemical findings with morphological classification? And, even more

importantly, what terminology do we base our morphological/histopathological classification upon?

Obviously, morphology only represents a single time point in an ongoing evolution within sub-RPE deposits. Therefore, it is not surprising to find transitional stages as well as different types of deposit next to each other. By light microscopy, two major entities of deposits can be distinguished: drusen, by definition, are located within Bruch's membrane—that is, beneath the basal lamina or basement membrane of the RPE, and can be further subclassified, according to their shape and structure. The majority of drusen are well circumscribed, especially the so called "hard" drusen. The "soft" or "confluent" type tends to be larger and less homogeneous. Quite often partial calcification of drusen can be observed in either variant. An entirely different type of deposit is found between the basement membrane and the cytoplasmic membrane of the RPE.

By light microscopy this deposit usually extends over a larger area than drusen and is in its advanced or "late" stage characterised by a linear palisade-like appearance, hence the original term basal linear deposit.^{11,12} There are strands of irregular material bridging Bruch's membrane and the elevated RPE. Usually, the overlying RPE remains intact, thus making the deposit invisible for the clinician on ophthalmoscopy. In a trichrome stain (particularly the Mallory), the deposit typically adopts the staining characteristics of collagen while in a periodic acid Schiff (PAS) stain it also reveals some staining properties of glycoproteins. By electron microscopy, the material starts as small excrescences on the basement membrane or the basal lamina of the RPE, so that it was logical to describe the abnormality as "basal laminar deposit". As the deposit progresses, one of the most obvious components is long spacing collagen,^{12,13} which is frequently found in aging basement membrane material in other parts of the body and also some ocular tissues (for example, in Descemet's membrane and in the trabecular meshwork, see also van der Schaft *et al*¹³). With further accumulation of extracellular material between the cell body and its basement membrane, the RPE eventually detaches completely in a shallow configuration over variably sized areas. Unfortunately, even at this stage there is no reliable clinical equivalent for this type of deposit because even advanced deposits still tend to be obscured by the RPE. The descriptive term for this deposit was first introduced by Sarks as basal *linear* deposit.¹¹ Sarks and her colleagues as well as others have demonstrated the frequent association of this deposit with choroidal neovascularisation and have stressed the importance in relation to disciform degeneration.^{11,14} Some time later for reasons explained above the deposit was renamed basal *laminar* deposit, while basal linear deposit was introduced as a term for vesicular material beneath the RPE basement membrane by Green and Enger.¹⁵ This caused considerable confusion, especially since the abbreviation *BLD* can represent both entities. In addition, van der Schaft *et al* equated basal laminar deposit (BLD) with long spacing collagen that only represents one component of the material and can occur on both sides of the RPE

basement membrane, thus neglecting the crucial difference of location and the various other substances within the BLD. In an attempt to reach an acceptable compromise and considering the staining properties and ultrastructural appearance of this material, we would therefore suggest the use of the term *basement membrane deposit* or *BMD* for the material located between the RPE cell and its basement membrane and to use the acronym BLD for the vesicular material located within Bruch's membrane (that is, between the basement membrane of the RPE and the inner collagenous zone), the most appropriate alternative term might then be "diffuse drusen" or "soft drusen".

Considering the relevance of individual types of sub-RPE deposits for the development of neovascular ARMD, there is general agreement in the literature about the morphology of deposits that are commonly seen in the presence of vascular proliferations beneath the RPE. As Green and Enger¹⁵ have convincingly shown, subretinal neovascularisation and disciform scars are most frequently associated with soft drusen and BMD. In our series, albeit smaller, we found similar results (Lee, unpublished data). There is significant photoreceptor loss associated with soft drusen and even more so with BMD, and the vast majority of disciform degeneration scars are found to contain strips of BMD. This has also been confirmed by ultrastructural studies of surgically excised subretinal membranes.¹⁶⁻¹⁸ The identification of the residue of diffuse drusen within neovascular scars is much more difficult.

At this point we feel that, in order to further study the pathogenesis of ARMD, the use of an unequivocal terminology of sub-RPE deposits is a prerequisite to any further investigations.

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- 1 Meyer A. Zur Entstehung der geschichteten Drusen der Lamina vitrea chorioideae. *Graefes Arch Ophthalmol* 1877;23:159-71.
- 2 Bressler NM, Silva JC, Bressler SB, et al. Clinicopathological correlation of drusen and retinal pigment epithelial abnormalities in age-related macular degeneration. *Retina* 1994;14:130-42.
- 3 International ARM Epidemiological Study Group. An international classification and grading system for age-related maculopathy and age-related macular degeneration. *Surv Ophthalmol* 1995;39:367-74.
- 4 Bressler SB, Maguire MG, Bressler NM, et al. The Macular Photocoagulation Study Group. Relationship of drusen and abnormalities of the retinal pigment epithelium to the prognosis of neovascular macular degeneration. *Arch Ophthalmol* 1990;108:1442-7.
- 5 Pauleikhoff D, Zuels S, Sheridah GS, et al. Correlation between biochemical composition and fluorescein binding of deposits in Bruch's membrane. *Ophthalmology* 1992;99:1548-53.
- 6 Holz FG, Sheridah G, Pauleikhoff D, et al. Analysis of lipid deposits extracted from human macular and peripheral Bruch's membrane. *Arch Ophthalmol* 1994;112:402-6.
- 7 Mullins RF, Johnson LV, Anderson DH, et al. Characterization of drusen-associated glycoconjugates. *Ophthalmology* 1997;104:288-94.
- 8 Kliffen M, Mooy CM, Luider TM, et al. Analysis of carbohydrate structures in basal laminar deposit in aging human maculae. *Invest Ophthalmol Vis Sci* 1994;35:2901-5.
- 9 Marshall GE, Konstas AG, Reid GG, et al. Type IV collagen and laminin in Bruch's membrane and basal linear deposit in the human macula. *Br J Ophthalmol* 1992;76:607-14.
- 10 Loeffler KU, Mangini NJ. Immunolocalization of ubiquitin and related enzymes in human retina and retinal pigment epithelium. *Graefes Arch Exp Clin Res* 1997;235:248-54.
- 11 Sarks SH. New vessel formation beneath the retinal pigment epithelium in senile eyes. *Br J Ophthalmol* 1973;57:951-65.
- 12 Loeffler KU, Lee WR. Basal linear deposit in the human macula. *Graefes Arch Clin Exp Ophthalmol* 1986;224:493-501.
- 13 Van der Schaft TL, de Bruijn WC, Mooy CM, et al. Is basal laminar deposit unique for age-related macular degeneration? *Arch Ophthalmol* 1991;109:420-4.
- 14 Spraul CW, Lang GE, Grossniklaus HE. Morphometric analysis of the choroid, Bruch's membrane, and retinal pigment epithelium in eyes with age-related macular degeneration. *Invest Ophthalmol Vis Sci* 1996;37:2724-35.
- 15 Green WR, Enger C. Age-related macular degeneration histopathologic studies. The 1992 Lorenz E. Zimmerman lecture. *Ophthalmology* 1993;100:1519-35.
- 16 Lopez PF, Grossniklaus HE, Lambert HM, et al. Pathologic features of surgically excised subretinal neovascular membranes in age-related macular degeneration. *Am J Ophthalmol* 1991;112:647-56.
- 17 Gehrs KM, Heriot WJ, de Juan E Jr. Transmission electron microscopic study of a subretinal choroidal neovascular membrane due to age-related macular degeneration. *Arch Ophthalmol* 1992;110:833-7.
- 18 Lee BL, Lim JJ, Grossniklaus HE. Clinicopathologic features of indocyanine green angiography-imaged, surgically excised choroidal neovascular membranes. *Retina* 1996;16:64-9.