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Bilaterality of drusen

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Abstract

The characteristics of drusen in 81 patients with bilateral drusen as a manifestation of age related disease were analysed for symmetry between the two eyes. It was found that there was close concordance with respect to drusen size, number, density, and fluorescence which was greater than would have been expected by chance alone. This finding implies that drusen may result from metabolic malfunction specific to the patient rather than the non-specific result of aging.

Loss of central vision in age related macular disease is due to lesions which occur in response to deposition of abnormal material in Bruch's membrane.[1] This abnormal material is believed to be derived from the retinal pigment epithelium.[2-6]

There is good evidence that the retinal pigment epithelial cells discharge cytoplasmic material throughout life into the inner portion of Bruch's membrane by apoptosis.[7-10] By this mechanism it is conceived that the pigment epithelium voids the products of phagosomal degradation and other metabolic activities. It is thought that the discharged material subsequently diffuses through Bruch's membrane and is cleared by the choroidal capillaries. The accumulation of debris in Bruch's membrane results from failure to clear the cytoplasmic contents deposited into this region. This may be due to changes in the fibres or inter-fibre matrix of Bruch's membrane whereby outward diffusion of material towards the choriocapillaris is hampered. In the dog it has been shown that Bruch's membrane impedes diffusion of only the largest molecules,[11] though decreased hydraulic conductivity occurs in man with age.[12] Alternatively it is possible that the material discharged into Bruch's membrane is abnormal, and in particular may contain large molecules and membrane complexes, such that free outward diffusion does not occur. Change in the nature of the material discharged into Bruch's membrane may reflect altered metabolism of the pigment epithelium, and in particular failure of the degradative lysosomal enzyme systems.

Discrete abnormal deposits in the inner portion of Bruch's membrane, when large, can be detected clinically as drusen.[13] Their appearance and distribution may vary widely from one patient to another, and histological studies imply that the composition of the deposits differs from one eye to another.[14,15] However, changes are rarely unilateral, and some symmetry exists between the right and left eyes for the number and type of drusen in the macula area.[16-20] In most of these studies limited data were obtained, and the aim of this project was to verify these observations. Drusen characteristics were analysed in order to examine whether or not symmetry of drusen exists between the two eyes of a patient which is greater than might have been expected by chance alone. If symmetry were proved, it would imply that drusen may result from metabolic changes specific to the patient rather than being non-specific results of aging.

Patients and methods

A retrospective study was undertaken of the clinical records, colour photographs, and fluorescein angiograms of a continuous series of 81 patients who were seen in 1983 and 1984 with the following attributes: all were over 50 years of age, they had minimal or no visual symptoms and good visual acuity, and had drusen at each macula but no signs of geographic atrophy, pigment epithelium detachment, or choroidal neovascularisation.

Photographs and angiograms of each patient were analysed by two authors independently for number, size, density, and early and late angiographic behaviour of the drusen by means of a grading scheme which has been described.[21,22] The posterior pole was divided into two areas: within (central) and outside (peripheral) 1600 μm of the foveola. The drusen in these areas were analysed according to their number (fewer than 10, 10 to 20, more than 20), their size (less than 50 μm, 50 to 500 μm, greater than 500 μm), and the distribution was classified as scattered, subconfluent, or confluent. Fluorescence of drusen was assessed as equal to choroidal fluorescence, slightly brighter than choroidal fluorescence, or brightly fluorescent during the dye transit and 3 minutes after dye entry. In most cases the drusen were uniform in size, distribution, and fluorescence in each area; when this was not the case the classification was determined by the largest, most densely

TABLE IA *Drusen number: central*

		Right eye			
	Number	*<10*	*10–20*	*>20*	*Total*
Left eye	0	5	0	0	5
	10–20	1	5	2	8
	<20	0	1	67	68
	Total	6	6	69	81

κ=0·82; standard error=0·08.

TABLE IB *Drusen number: peripheral*

		Right eye				
	Number	*0*	*<10*	*10–20*	*>20*	*Total*
Left eye	0	10	0	0	0	10
	<10	1	11	4	1	17
	10–20	0	3	7	3	13
	>20	0	0	0	41	41
	Total	11	14	11	45	81

κ=0·77; standard error=0·07.

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TABLE IIA *Drusen size: central*

		Right eye			
	Size	*1*	*2*	*3*	*Total*
Left eye	1	8	2	0	10
	2	1	55	5	61
	3	0	0	10	10
	Total	9	57	15	81

κ=0·77; standard error=0·07

TABLE IIB *Drusen size: peripheral*

		Right eye				
	*Size**	*0*	*1*	*2*	*3*	*Total*
Left eye	0	10	0	0	0	10
	1	0	14	4	0	18
	2	1	7	44	1	53
	3	0	0	0	0	0
	Total	11	21	48	1	81

κ=0·70; standard error=0·08

*0=no drusen. 1=<50μm. 2=50–500 μm. 3=>500 μm.

TABLE IVA *Drusen early fluorescence: central*

		Right eye			
	Grade	*1*	*2*	*3*	*Total*
Left eye	1	2	0	0	2
	2	1	4	0	5
	3	0	0	7	7
	Total	3	4	7	14

κ=0·89; standard error=0·18

TABLE IVB *Drusen early fluorescence: peripheral*

		Right eye				
	*Grade**	*0*	*1*	*2*	*3*	*Total*
Left eye	0	1	0	0	0	1
	1	0	1	0	0	1
	2	0	1	4	0	5
	3	0	0	0	7	7
	Total	1	2	4	7	14

κ=0·89; standard error=0·18

*0=no drusen. 1=equal to choroidal fluorescence. 2=slightly brighter than choroidal fluorescence. 3=brightly fluorescent.

packed, and most fluorescent lesions. If the two readers disagreed, a third observer was asked to arbitrate, and the results were assigned after discussion.

The clinical data and the results of the drusen analysis were recorded and subjected to statistical analysis. The reliability of the assessment was examined by recording the percentage agreement between the two independent observers. Kappa statistics were used to assess the symmetry between the right and the left eye. These statistics evaluate the observed concordance beyond chance, related to the maximum possible agreement in excess of chance.[23] In most situations a κ value of 0·8 indicate almost perfect concordance, and κ values of 0·61–0·80 suggest substantial symmetry.[24]

Results

Of the 81 patients 48 were females and 33 males. The average age of presentation was 61·3 years, range 50 to 81 years.

The interobserver reliability was 92·7% for the number, 93·9% for size, 89·6% for density, and 96·2% and 97·6% for early and late fluorescence of drusen.

Despite the presence of clustering, there was manifest symmetry between the two eyes for drusen size, density, and number which was greater than would have been expected by chance alone (Tables I–III).

Because early pictures of fluorescein angiograms in both eyes were not available for most patients, the analysis of symmetry for this characteristic is based only on the data from 14 patients. Despite this, symmetry was demonstrated between the two eyes in the central and peripheral areas of the macula (Table IV). For the analysis of the late fluorescein angiograms of both eyes 52 patients were available. The concordance between the right eye and the left was excellent in the central and peripheral parts of the macula (Table V).

Discussion

For all analysed drusen characteristics the interobserver reliability was between 80% and 95%, which is comparable with the findings in other studies[25] and is considered to be an acceptable degree of agreement to justify conclusions.[26]

The results of our analysis recorded a good or excellent symmetry for all ophthalmoscopic and fluorescein angiographic characteristics of drusen in the central and peripheral areas of the

TABLE IIIA *Drusen density: central*

		Right eye			
	Grades	*1*	*2*	*3*	*Total*
Left eye	1	8	1	0	9
	2	1	42	7	34
	3	0	4	18	22
	Total	9	47	25	81

κ=0·71; standard error=0·09

TABLE IIIB *Drusen density: peripheral*

		Right eye				
	*Grade**	*0*	*1*	*2*	*3*	*Total*
Left eye	0	10	0	0	0	10
	1	0	30	4	0	34
	2	1	3	29	0	33
	3	0	0	2	2	4
	Total	11	33	35	2	81

κ=0·81; standard error=0·08

*0=no drusen. 1=scattered. 2=subconfluent. 3=confluent.

TABLE VA *Drusen late fluorescence: central*

		Right eye			
	Grade	*1*	*2*	*3*	*Total*
Left eye	1	2	0	0	2
	2	0	17	1	18
	3	0	0	32	32
	Total	2	17	33	52

κ=0·89; standard error=0·18

TABLE VB *Drusen late fluorescence: peripheral*

		Right eye				
	*Grade**	*0*	*1*	*2*	*3*	*Total*
Left eye	0	5	0	0	0	5
	1	0	1	0	0	1
	2	0	0	10	2	12
	3	0	0	0	34	34
	Total	5	1	10	36	52

κ=0·95; standard error=0·10

*0=no drusen. 1=equal to choroidal fluorescence. 2=slightly brighter than choroidal fluorescence. 3=brightly fluorescent.

posterior pole between both eyes in each patient. These observations are in accord with previous observations of bilateral incidence[17 19 20] as well as ophthalmoscopic assessment of symmetry.[16 18 20] Most striking was the symmetry of fluorescence between the two eyes, an attribute not investigated previously.

These findings have relevance to the concepts concerning drusen formation with age. The symmetry between the two eyes, despite the wide variation from one patient to another, implies that there is a degree of specificity in the determinants of disease. It is evident that the structural or metabolic characteristics which result in drusen formation have regional as well as quantitative variation peculiar to the individual. There is evidence that the degree of fluorescence of drusen gives some indication of their chemical composition.[14] If this is the case, the angiographic characteristics also imply that the chemical composition of drusen is patient specific. That there may be specific determinants of drusen formation would be in contrast with the view that accumulation of debris in Bruch's membrane is a non-specific age change. However, it is unlikely that the failure involves isolated metabolic systems alone, since there is considerable clustering of data. It is more likely that the changes represent the result of a spectrum of metabolic abnormalities, but that the two eyes of an individual share the same attributes.

These findings also have clinical relevance. Symmetry of drusen would explain the high risk of fellow eyes in patients with unilateral visual loss when compared with the risk in a patient with bilateral drusen.[18 22 27 28] The number and type of drusen are important in determining the magnitude of risk,[18 22 26-29] so that the circumstances which caused the complication in one eye would also pertain in the fellow eye. Moreover, it has been shown that the attributes of drusen determine the nature of the lesion causing visual loss.[21] On this basis one would predict that the similarity of drusen between two eyes would result in symmetry of the precise complication of age related macular disease. In one study such symmetry was found.[30]

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