Serum immunoglobulins in retinal vasculitis

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Perivasculitis is a common pathological reaction in the retina, the veins being affected more frequently than the arteries. It is not a specific disease entity and the majority of cases are thought to result from an allergic reaction to one of a wide variety of antigens (Ashton, 1962). Reviews of the subject have been published by Donders (1958), Godd-Jolly (1961), Doden (1963), Koliopoulos (1967), Duke-Elder and Dobree (1967), and Charamis (1968).

Clinical and experimental observations strongly suggest that allergic mechanisms play a predominant role in retinal vasculitis (Uyama, 1936; Meyer, 1940; De Muro and Focosi, 1951; Elliot, 1954; Miescher, Paronetto, Borel, and Miescher, 1968). Treatment with immunosuppressives (cortisone, etc.) gives good results, as shown by Elliot (1962) and Cross (1965). Retinal vasculitis can be associated with other ocular or systemic diseases in which immune reactions are probably involved, such as uveitis, Behet's disease, sarcoidosis, multiple sclerosis, etc., or with infective conditions, such as tuberculosis and brucellosis.

From a clinical and aetiological point of view, retinal vasculitis can be divided into three distinct types:

- (a) Secondary to uveitis;
- (b) Secondary to systemic disease;
- (c) A primary type the aetiology of which is largely conjectural since in most cases no specific cause can be found (Duke-Elder and Dobree, 1967).

This preliminary study was undertaken in an attempt to discover whether there is any correlation between the clinical picture of retinal vasculitis and the humoral components of the immune system.

Material and methods

The serum immunoglobulins of thirteen patients with retinal vasculitis were estimated, using the single radial immunodiffusion plate method as described by Mancini, Carbonara, and Heremans (1965). The normal levels of serum globulins in the control group of healthy adults, obtained by the same method in the same laboratory, were:

For γ G* (or IgG) 700 to 1,500 mg./100 ml. serum;

For γ A (or IgA) 150 to 450 mg./100 ml. serum;

For γ M (or IgM) 50 to 150 mg./100 ml. serum.

Table I shows a comparison of these levels with the mean values obtained by other workers using similar techniques.

Table I Mean values of immunoglobulins (mg./100 ml. serum) as assayed by simple radial immunodiffusion

Authors	Date	Immunoglobulins		
		γ G	γ A	γ M
Mancini and others	1965	1,200	243	146
McKelvey and Fahey	1965	1,240	280	116
Stiehm and Fudenberg	1966	1,158 $\pm$ 305 (569-1,919)	200 $\pm$ 61 (61-330)	99 $\pm$ 27 (47-147)
Aiuti, Turbessi, Cirelli, de Bac, Martinelli, and Ricci	1967	1,160	177	97
Zanussi and Medina	1967	1,172 $\pm$ 190	245 $\pm$ 190	105 $\pm$ 11
Johnson and Bloch	1969	1,180 $\pm$ 310	218 $\pm$ 96	98 $\pm$ 41
Our normal limits		700-1,500	150-450	50-150

The patients had been followed up for 6 months or more, but investigations had not confirmed any specific aetiology. Those in whom a specific diagnosis was established, *e.g.* toxoplasmosis, rheumatoid arthritis, or other systemic disease, were excluded. The series included cases of primary retinal vasculitis and vasculitis secondary to an active or an old uveitis. The cases of primary vasculitis were divided into two types:

- (a) Peripheral, more closely resembling the classical picture of Eales's disease;
- (b) Central, of the type described by Lyle and Wybar (1961).

Some of the patients with the central type had been diagnosed initially as having a central vein thrombosis, but the rather low age range (27 to 47 years), the retention of good vision, and the ophthalmoscopic picture suggested a central type of vasculitis.

Results

The concentrations of the three major immunoglobulins (γ G, γ A, γ M) determined by the radial immunodiffusion method in the thirteen patients are shown in Table II (opposite).

The immunoglobulin levels in those with the central type of vasculitis were within normal limits, except in Case 4 in whom the γ M was raised. In cases of peripheral vasculitis, the γ M levels were near the lower limit of normal, and Case 7 had a very low value (25 mg./100 ml. serum). By contrast, all four with vasculitis secondary to uveitis had serum concentrations of γ M above the limit of normal.

Discussion

The responses of the immune system can be broadly divided into two groups, humoral and cellular. The humoral antibody responses are based on antibody molecules, the immunoglobulins γ G, γ A, γ M, γ D, γ E (in decreasing order of concentration). These are synthesized by immunologically activated cells. The cellular immune responses are carried out by sensitized cells, mainly lymphocytes. Estimation of the serum levels of immunoglobulins indicates the degree of the patient's immunological response as far as humoral antibodies are concerned.

If retinal vasculitis is the result of an allergic reaction, some alteration of circulating antibodies might be expected in patients with this condition. Johnson and Bloch (1969) reported a series of four patients with Eales's disease in whom the mean level of γ G was

* The terminology is that suggested by the World Health Organization Nomenclature Committee (*Bull. Wld Hlth Org.*, **30**, 447, 1964).

Symbols proposed

γ G or IgG

γ A or IgA

γ M or IgM

Previous usage

γ , γ S γ , 6-6S γ , γ S, γ ss

β 2A, γ 1A

γ 1M, β 2M, 19S γ , γ -macroglobulin

Table II Serum immunoglobulin concentrations (mg./100 ml.) in patients with retinal vasculitis

Type of vasculitis	Case no.	Sex	Age (yrs)	Immunoglobulins		
				γG	γA	γM
Central	1	F	47	1,150	350	75
	2	M	38	1,050	425	130
	3	M	27	1,000	380	82
	4	F	32	1,050	187	165
Means				1,062	336	118
Peripheral (Eales's disease)	5	M	31	1,000	150	67
	6	M	24	1,200	210	70
	7	F	62	720	230	25
	8	M	40	1,300	390	62
	9	M	34	880	380	80
Means				1,020	252	61
Secondary to uveitis	10	F	39	1,000	80	400
	11	M	32	920	310	160
	12	M	30	1,100	225	160
	13	F	23	1,300	175	155
Means				1,080	198	219
Controls				700-1,500	150-450	50-150

raised (1,512 mg./100 ml. $\pm$ 259) but in whom the γ M levels were within normal limits (70-145 mg./100 ml.). In our series the γ G immunoglobulins were not increased in Eales's disease, but the mean level of the γ M immunoglobulins was low, and one patient had only 25 mg./100 ml. serum.

The most striking finding in our series concerned patients in whom the vasculitis was considered to be secondary to uveitis. All four had raised levels of γ M immunoglobulin. Raised γ M levels have been reported in uveitis by Aronson (1968), but as an elevation of γ M occurs in many virus infections it is difficult to postulate any specific relation between uveitis and abnormal immunoglobulins on the basis of the present evidence. One of our patients with uveitis had a low serum γ A level, but the significance of this finding is not known.

Uveitis is often associated with connective tissue disorders (Duke-Elder and Perkins, 1966), but there was no evidence of such an association in this series. It may be that the high levels of γ M represent an increase in antibody to an unrecognized micro-organism or other antigen. On the other hand it is possible, as Aronson (1968) suggested, that individuals with high levels of γ M are more susceptible to uveitis. Our results and those of other workers suggest that further investigation of the immunological responsiveness of patients with uveitis and retinal vasculitis would be worthwhile.

Summary

In thirteen cases of retinal vasculitis the serum immunoglobulins were determined by the single radial immunodiffusion method. An elevation of γ M was found in four cases secondary to uveitis. In the central type of retinal vasculitis the levels of the three major

immunoglobulins (γ G, γ A, γ M) were within normal limits, but in cases of the peripheral type (Eales's disease) a low level of γ M was found. The significance of these results is discussed.

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