

Rational Management of Uveitis

E. ANCKER, A. C. B. MOLTENO, J. L. STRAUGHAN

SUMMARY

Endogenous uveitis is an important cause of blindness in young adults. The need for a comprehensive search for an aetiological 'antigen' is stressed. A source of adjuvant, disturbance in host immunology and any associated syndromes are also sought. Treatment then involves elimination of 'antigen', suppression of host hypersensitivity and the enhanced vascular permeability, and improvement of host resistance. The value of antihistamine and anti-serotonin drugs in successful treatment is emphasised.

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Endogenous uveitis is a major cause of blindness and is particularly important because it affects mainly young adults. The average case can be treated empirically with steroids and atropine and a broad-spectrum antibiotic with good immediate effect. However, the patient so treated in whom the disorder recurs, will not do so well, and the chances of establishing an aetiology are then much smaller. In this article we present a rational scheme of management for uveitis.

APPROACH AND METHODS

Our approach is to identify the cause, or the combination of factors, responsible for the uveitis. This is not always possible, but by using a variety of clinical, biochemical and bacteriological investigations, and by interpreting these in the light of standard immunological theory, we are able to investigate and treat endogenous uveitis in a rational manner. We do a complete examination of the patient at a special uveitis clinic. Our approach is based on the general proposition that the lesion of endogenous uveitis is caused by an 'antigen' which may range from hapten, virus, fungus, protozoon through to the patient's bodily constituents. In addition, the patient's immunological response is influenced by adjuvants and various general diseases. These factors can be conveniently summarised by the equation:

$$\text{size of lesion} = \frac{\text{antigen dose} \times \text{multiplying power} \times \text{host hypersensitivity}}{\text{body resistance}}$$

Departments of Ophthalmology and Pharmacology, University of Stellenbosch and Tygerberg Hospital, Parowvallei, CP

E. ANCKER, M.B. CH.B., M.D., M.MED.(OPHTHAL.)

A. C. B. MOLTENO, M.B. CH.B., F.R.C.S.

J. L. STRAUGHAN, M.B. CH.B., B.SC. HONS

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We therefore attempt to identify a source of antigen, a source of adjuvant, disturbed immunological response of the host and any associated syndromes (Table I).

Table II gives the spectrum of diseases which are commonly associated with uveitis in the Western Cape.

TABLE I. UVEITIS INVESTIGATIONS

X-ray examination

Skull
Sinuses
Teeth
Chest
Lumbar sacral spine

Indirect tests

ESR, FBC
Immuno-electrophoresis
C-reactive protein
Liver functions
Urea, uric acid
Mucoprotein

Specific tests

VDRL
FTA-ABS } for syphilis
RPR
Gonococcal complement fixation
ASO-titre
Widal
Weil-Felix
Brucella
Paul-Bunell
Histoplasmosis
Leptospirosis
Toxoplasmosis
Tuberculin skin tests: tine, Mantoux

Specialist opinion

ENT
Urology
Gynaecology
Internal medicine

Treatment

Treatment involves elimination of antigen, suppression of host hypersensitivity and improvement of host resistance. Although the antigen may be easily and quickly identified, e.g. toxoplasmosis or syphilis, it is very important to suppress the inflammation as soon as possible, in order to prevent the development of auto-antibodies to the lens, the retina and possibly the uvea, or, what is probably more important, the accumulation of large numbers of immunocytes within the eye tissue.

TABLE II. RESULTS OF INVESTIGATION OF 122 CASES OF ENDOGENOUS UVEITIS

Idiopathic	Presumptive	Strongly presumptive	Proven
26	Strep. infections 32	Syphilis 7	Retinal detachment 3
	Syphilis 15	Tuberculosis 8	Sarcoidosis 2
	Toxoplasmosis 1	Toxoplasmosis 6	Bronchopneumonia 2
	Tooth abscess 5	Angle closure glaucoma 2	
	Amoebiasis 3	Herpes simplex 2	
	Typhoid 2	Fuchs heterochromia 2	
	Lens-induced 1	Rickettsia 1	
		Salmonellosis 1	
		Gonorrhoea 1	
—	—	—	—
26	59	30	7

Steroids, which are the mainstay of anti-inflammatory therapy, are effective in preventing the development of immunocytes from small lymphocytes, but once immunocytes have developed, they are much less effective.

We have found that when steroids alone have failed to control intra-ocular inflammation, inhibitors of serotonin and histamine have been effective.

CASE REPORTS (Table III)

Case 1

A woman whose right eye had been destroyed during childhood, developed a grumbling uveitis in the remaining eye at the age of 55 years. After 7 years the condition produced a dislocated lens and uncontrollable glaucoma. Two Scheie operations failed to control the pressure, but control was attained by a Molteno implant inserted in May 1970. However, the uveitis remained active, and

by December 1973 it was uncontrolled in spite of systemic treatment with steroids and subconjunctival Depo-Medrol every 3 weeks. Side-effects of steroids — hypertension, gastric discomfort and collapse of a vertebra — were becoming intolerable. A trial of methysergide maleate (Deseril) and chlorpheniramine maleate (Chlortrimeton) was commenced and she has responded dramatically so far. The patient has been discharged and is treated as an out-patient. A relapse followed on one occasion when she ran out of medication, but for the last 12 months her uveitis has been controlled with Chlortrimeton and Deseril, and Depo-Medrol administered subconjunctivally once a month. Systemic treatment with steroids has not been necessary.

Case 2

A 12-year-old girl presented with recurrent bilateral non-granulomatous uveitis, associated with a rising anti-streptolysin titre and a streptococcal infection of her upper

TABLE III. RESULTS OF 8 CASES OF SEVERE UVEITIS TREATED WITH DESERIL AND CHLORTRIMETON

Patient	Diagnosis	Not controlled by	Controlled by
1	Granulomatous panuveitis Lens-induced	Prednisone Depo-Medrol	Deseril Chlortrimeton Depo-Medrol
2	Non-granulomatous panuveitis Streptococcal infection	Penicillin Depo-Medrol	Deseril Chlortrimeton
3	Non-granulomatous posterior uveitis Ankylosing spondylitis	Antibiotics Depo-Medrol Prednisone	Deseril Chlortrimeton
4	Non-granulomatous anterior uveitis Streptococcal infection	Antibiotics Depo-Medrol	Deseril Chlortrimeton
5	Granulomatous panuveitis No cause found	Prednisone Antibiotics Depo-Medrol (worsened)	Deseril Chlortrimeton
6	Granulomatous panuveitis Pyelonephritis	Antibiotics Depo-Medrol (worsened)	Deseril Chlortrimeton
7	Non-granulomatous posterior uveitis No cause found	Depo-Medrol Prednisone Antibiotics	Deseril Chlortrimeton
8	Granulomatous panuveitis No cause found	Depo-Medrol (worsened) Antibiotics	Deseril Chlortrimeton

respiratory tract. In spite of her tonsils having been removed, long-term treatment with penicillin and systemic, subconjunctival and local treatment with steroids, the disease remained very active. She responded to Deseril and Chlortrimeton. Steroids were withdrawn completely, and her uveitis is being controlled with long-term treatment with penicillin administered systemically. Deseril and Chlortrimeton were discontinued after 3 months, and the patient has not suffered a relapse for 8 months.

Other patients have been treated in the same way, with similar results.

DISCUSSION

An initial attack of uveitis may be induced by a single exposure to a large amount of antigen, which excites an immune response. The antibody which is thus produced combines with the antigen to form soluble circulating immune complexes^{1,2} which are deposited at multiple sites, including the eye, to cause immune complex uveitis, (e.g. uveitis associated with serum sickness). However, severe and recurrent attacks of uveitis are generally not associated with systemic immune disease, while histological examination of inflamed eyes shows large numbers of immunocytes within the uveal tissues. These cells (small lymphocytes and plasma cells), which are known to remain for long periods in tissue spaces, produce antibodies and when triggered by fresh circulating antigen cause a severe local inflammatory reaction on an immune basis.

These concepts suggested to us that patients with severe or recurrent uveitis could be treated by preventing contact of intravascular circulating antigen with immunocytes in the interstitial fluid of the ocular tissues, through the use of suitable antagonists of the vascular permeability factors. Increased vascular permeability in inflammation³ is induced by mediators such as histamine, serotonin, kinins, acetylcholine and the prostaglandins. It is thought that these mediators are activated in a definite sequence, starting with histamine or serotonin, which are the mediators of the immediate-type permeability response⁴⁻⁶ and continuing with kinins which seem to be the final mediators of the delayed permeability response,^{7,8} and the prostaglandins, which are associated with the later stages of more severe grades of inflammation.^{9,10}

Animal research in which auto-immune glomerulonephritis in rabbits was used as a model of inflammation has demonstrated the involvement of histamine and serotonin in deposition of antigen antibody complexes in immune complex disease. Antagonists of these blood permeability

factors largely prevent acute immune complex disease in the rabbit^{11,12} and in man.¹³ In the chronic model of immune complex disease in the rabbit^{14,15} much greater quantities of complexes become deposited in the kidneys than in the acute model.¹⁶ Kniker has reported diminished deposition of immune complexes with decrease in the resultant injury after treatment with antagonists of histamine and serotonin.¹⁷ We have used an antiserotonin, methysergide maleate (Deseril) and an antihistamine, chlorpheniramine maleate (Chlortrimeton), in cases where steroids alone were ineffective.

In these desperate cases we have treated the patients with Chlortrimeton and Deseril on a long-term basis (3-12 months). These drugs are well tolerated and we have had no serious side-effects. Deseril may produce weakness, nausea, diarrhoea, angina, claudication, oedema, tingling of extremities, psychosis and retroperitoneal fibrosis. Chlortrimeton may cause drowsiness, dizziness, dry mouth, nausea, headaches, muscular twitching, and rarely hyperpyrexia. An alternative regimen with relatively non-toxic cyproheptadine hydrochloride (Periactin) which was also effective in rabbits but to a lesser degree than the chlorpheniramine-methysergide combination,¹⁷ was tried, but found to be useless in humans.

In conclusion, we wish to emphasise that while the combination of antihistamine and a serotonin antagonist is very effective in the special circumstances found in cases of endogenous uveitis, it should be used with great care in selected cases, especially when long-term administration is contemplated.

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