Immune Deposits in Iris Biopsy Specimens From Patients With Fuchs' Heterochromic Iridocyclitis

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To investigate whether Fuchs' heterochromic iridocyclitis may be an immune complex vasculitis, we used an immunofluorescence technique to detect immunoglobulins and complement in iris biopsy specimens from nine patients with Fuchs' heterochromic iridocyclitis, 12 patients with other types of uveitis, and nine patients with glaucoma but without uveitis. No specific immune deposits were observed in the irises of the patients with Fuchs' heterochromic iridocyclitis. Immunoglobulin G, IgA, IgM, and complement were detected in patients with Fuchs' heterochromic iridocyclitis and patients with uveitis, and these results differed significantly ($P < .05$) from the group without uveitis. The immune deposits were found only in the iris vessel walls. No light-microscopic evidence of an inflammatory vascular process could be detected. Further studies are necessary to investigate whether the immune reactants originate from the circulation or result from local formation.

FUCHS' HETEROCHROMIC IRIDOCYCLITIS is still a distinct clinical entity of unknown origin. It is characterized by a mostly unilateral, chronic, low-grade anterior uveitis and a variable degree of atrophy and depigmentation of the iris stroma and pigment epithelium. Other typical findings include the widely scattered small keratic precipitates and the absence of synechiae. Subcapsular cataract is often present and

Fuchs' heterochromic iridocyclitis is complicated by glaucoma in 15% to 20% of cases.¹⁻⁴

A vascular pathogenesis involving the iris vessels is one of the hypotheses for the cause of Fuchs' heterochromic iridocyclitis.⁵ The characteristic filiform hemorrhage seen after anterior chamber paracentesis (Amsler's sign) was the first vascular abnormality described in patients with this disease.⁶ Later, iris fluorescein angiographic studies showed distinct, mainly peripupillary fluorescein leakage, delayed filling, and sectors of ischemia frequently associated with neovascularization.^{7,8}

Light microscopy disclosed abnormal hyalinization and sometimes endothelial proliferation of the iris vessel walls, with narrowing of the vessel lumen.^{1,5,9,10} This narrowing of the vessel lumen, ultimately leading to occlusion, may be the result of immune complex deposition, and Fuchs' heterochromic iridocyclitis may be an immune complex vasculitis.^{5,11}

Immune complexes have been detected in the aqueous humor and serum of patients with Fuchs' heterochromic iridocyclitis.^{12,13} Plasma cells^{9,14-19} present in the iris may be responsible for the local production of antibodies, subsequently leading to intraocular immune complex formation.^{5,10}

Little evidence has been provided concerning an immune complex vasculitis of the iris vessels in patients with Fuchs' heterochromic iridocyclitis. We investigated this hypothesis by using an immunofluorescence technique to demonstrate deposits of immunoglobulins and complement in iris biopsy specimens from patients with Fuchs' heterochromic iridocyclitis. Results were compared with those of patients without uveitis and of patients with other types of uveitis.

Material and Methods

Iris biopsy specimens (from peripheral iridectomies) were obtained from nine patients with

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Fuchs' heterochromic iridocyclitis (mean age $\pm$ standard deviation, 39.1 ± 15.9 ; range, 25 to 77 years; four women and five men), and 12 patients with other types of uveitis (mean age $\pm$ standard deviation, 56.1 ± 21.6 ; range, 22 to 88 years; eight women and four men), classified according to the recommendations of the International Uveitis Study Group.²⁰ Diagnoses included chronic anterior uveitis (four patients, in one of whom the uveitis was associated with juvenile chronic arthritis), recurrent anterior uveitis (three patients, in two of whom the uveitis was associated with HLA-B27), idiopathic panuveitis (four patients), and one patient with phacogenic uveitis. At the time of the operation, no patients with Fuchs' heterochromic iridocyclitis were being treated systemically, but two were using corticosteroid eyedrop preparations, and one was using antiglaucoma eyedrops. Of the 12 patients with other types of uveitis, two were being treated with systemic noncorticosteroid anti-inflammatory drugs, seven were being treated with corticosteroid eyedrop preparations, and three patients were being treated with antiglaucoma eyedrops at the time of the operation.

Iris specimens were also obtained from nine patients without uveitis (mean age $\pm$ standard deviation, 58.6 ± 17.5 ; range, 31 to 83 years; five women and four men) who had primary open-angle glaucoma and were undergoing trabeculectomy. None of these patients was treated systemically and all patients were using antiglaucoma eyedrops at the time of the operation. We chose patients with glaucoma as controls, rather than patients undergoing extracapsular cataract extraction for nuclear age-related cataract, because peripheral iridectomy is an integral part of trabeculectomy. All patients were informed of these investigations and their consent was obtained.

All specimens were snap-frozen in optimal cutting-tissue compound within one hour of iridectomy. Four-micrometer-thick cryostat sections were fixed in acetone for ten minutes and subsequently air-dried and rinsed in phosphate-buffered saline solution (pH, 7.4). Slides were then incubated for one hour at room temperature (20 C) with a panel of polyclonal rabbit antibodies in phosphate-buffered saline solution containing 0.02% gelatin and 0.1% sodium azide. The following antibodies were used: antihuman IgG, IgA, and IgM, all labeled with fluorescein isothiocyanate (De Beer Medicals, Hilvarenbeek, The Netherlands), used in a direct (one-step) method, and antihuman com-

plement (C3c + C3d + C4), fibrinogen, C1q, and C3 (Central Laboratory of the Red Cross Blood-transfusion Service, Amsterdam, The Netherlands) used in an indirect (two-step) method. Normal rabbit serum (Dakopatts, Glostrup, Denmark) was used as a negative control. For the second step, after rinsing the slides in phosphate-buffered saline solution, they were incubated for one-half hour at room temperature (20 C) with fluorescein isothiocyanate-labeled polyclonal horse antirabbit immunoglobulins. Subsequently, all slides were rinsed in phosphate-buffered saline solution.

One slide from each specimen was stained with hematoxylin and eosin to evaluate the following pathologic features typical of Fuchs' heterochromic iridocyclitis: (1) the presence of inflammatory cells; (2) iris stromal atrophy and fibrosis; (3) disappearance of stromal melanocytes; (4) focal depigmentation of the iris pigment epithelium; and (5) hyalinization of the vessel walls, as described in an earlier study.²¹ This stain was also used for the evaluation of the light-microscopic signs characteristic of vasculitis. These clinical signs are defined as neutrophilic or lymphocytic and plasmacellular invasion of the vessel wall with fibrinoid necrosis or fibrous thickening.^{22,23}

Tissue sections were examined with a fluorescence microscope using a $\times 25$ magnification in a masked fashion by two of us (E.L.H. and C.M.M.) who were unaware of the diagnosis. Immunofluorescence staining in a granular pattern in the vessel wall was considered positive, whereas it was considered negative in the absence of fluorescence or if a homogeneous staining pattern resulting from diffusion of plasma from the lumen was present. Comparison between the three groups was performed by using the Fisher's exact test.

Results

The granular deposition of immunoglobulins, complement, and fibrinogen in the vascular walls of the iris vessels in the iris biopsy specimens of all groups was determined (Table). No extracellular immune deposits were observed outside the vessel walls. The findings in patients with Fuchs' heterochromic iridocyclitis did not differ significantly from those in patients with other types of uveitis.

Immunoglobulin G, IgA, C3, fibrinogen ($P < .05$), IgM ($P < .01$), and complement ($P = .001$)

TABLE
IMMUNE DEPOSITS IN IRIS VESSEL WALLS OF PATIENTS WITH FUCHS' HETEROCHROMIC IRIDOCYCLITIS, PATIENTS WITH UVEITIS, AND PATIENTS WITH GLAUCOMA

IMMUNE DEPOSITS	NO. OF DEPOSITS IN PATIENTS WITH FUCHS' HETEROCHROMIC IRIDOCYCLITIS (N=9)	DIFFERENCE*	NO. OF DEPOSITS IN PATIENTS WITH UVEITIS (N=12)	DIFFERENCE†	NO. OF DEPOSITS IN PATIENTS WITH GLAUCOMA (N=9)
IgG	4	P = .041	1	P = .571	0
IgA	4	P = .041	4	P = .083	0
IgM	7	P = .007	6	P = .072	1
Complement	7	P = .001	5	P = .039	0
C1q	2	P = .235	3	P = .165	0
C3	4	P = .041	4	P = .083	0
Fibrinogen	4	P = .041	6	P = .017	0

*Difference between patients with Fuchs' heterochromic iridocyclitis and patients with glaucoma.

†Difference between patients with uveitis and patients with glaucoma.

were found in a significantly higher number of irises obtained from patients with Fuchs' heterochromic iridocyclitis than in irises obtained from patients with glaucoma but without uveitis (Fig. 1). Complement and fibrinogen were the only immune deposits found in a significantly higher ($P < .05$) number of irises from patients with uveitis than in irises obtained from patients with glaucoma but without uveitis (Fig. 2). Plasma cells containing IgG, IgA, or IgM were found in the iris stroma of four of nine irises obtained from patients with Fuchs' heterochromic iridocyclitis and in six of the 12 irises from patients with uveitis. Immunoglobulin G, IgA, and IgM were equally distributed in the plasma cells of both groups. No immunoglobulin-containing plasma cells could be detected in the irises obtained from patients with glaucoma but without uveitis.

No correlation could be seen between those patients treated with corticosteroids and the presence or absence of specific immune deposits. However, in the two patients with uveitis who were treated with systemic noncorticosteroid anti-inflammatory drugs, no immune deposits were found.

Pathologic features typical of Fuchs' heterochromic iridocyclitis (Fig. 3) were observed with hematoxylin and eosin staining in eight of the nine irises obtained from patients with Fuchs' heterochromic iridocyclitis. No characteristics of vasculitis were observed by light microscopy in any of the iris biopsy specimens. Scattered deposits of infiltrating mononuclear cells (chiefly lymphocytes and plasma cells) were observed in the iris stroma and anterior

iris border layer, but not in the vessel walls, of all irises obtained from patients with Fuchs' heterochromic iridocyclitis or uveitis. In six of the nine irises from control patients (patients with glaucoma but without uveitis), a few isolated mononuclear cells were observed in the iris stroma. Hyalinization of the iris vessel walls was observed in the irises of all patients with Fuchs' heterochromic cyclitis or uveitis. The vessel walls of four irises from patients with glaucoma also had some degree of hyalinization. No endothelial proliferation of the iris vessel walls was found in any of the iris biopsy specimens.

Discussion

Deposits of immunoglobulins and complement were observed in the vessel walls of the irises of patients with Fuchs' heterochromic iridocyclitis. However, no specific immunofluorescence staining pattern could be identified in the irises of patients with Fuchs' heterochromic iridocyclitis. The immune deposits observed in patients with Fuchs' heterochromic iridocyclitis were similar to those found in the patients with uveitis.

Although the only acceptable proof for the demonstration of immune complexes is the detection of the antigen involved, the deposition of both immunoglobulins and complement suggests the presence of immune complexes in the vessel walls of the iris. These immune complexes may either be formed within the eye or result

Fig. 1 (La Hey and associates). Iridectomy specimen from a patient with Fuchs' heterochromic iridocyclitis. Left, Granular IgM deposits in vessel wall ($\times 630$). Right, Granular IgA deposits in vessel wall ($\times 630$).

from the deposition of circulating immune complexes in the iris vessel walls.

Earlier studies demonstrated circulating immune complexes in the serum and aqueous humor of patients with Fuchs' heterochromic iridocyclitis.^{11,12} Circulating immune complexes are associated with many autoimmune diseases. Recently detected cellular and humoral immunity directed against corneal antigens suggest a role of autoimmune reactions in the pathogenesis of Fuchs' heterochromic iridocyclitis.^{24,25} However, patients with Fuchs' heterochromic iridocyclitis are generally free of the more commonly encountered systemic manifestations of immune complex disease such as arthritis, glomerulonephritis, or scleritis.⁵ Moreover, in patients with systemic vasculitic syndromes such as systemic lupus erythematosus, ocular manifestations are uncommon.²⁶ It is

difficult to implicate circulating immune complexes in a disease that is usually unilateral, unless there are conditions of the vessel walls of the already affected iris that promote binding of immune complexes.⁵

The typical perivascular distribution of the immune deposits and the absence of these deposits in the surrounding iris tissue suggest that the immune reactants originate from the circulation and are not formed within the iris stroma. Because the presence of the immune deposits was limited to the vessel walls, it seems likely that, if circulating immune complexes are involved in the pathogenesis of Fuchs' heterochromic iridocyclitis, these com-

Fig. 2 (La Hey and associates). Iridectomy specimen from a patient with idiopathic recurrent anterior uveitis. Granular fibrinogen deposits in vessel walls ($\times 400$).

Fig. 3 (La Hey and associates). Iridectomy specimen from a patient with Fuchs' heterochromic iridocyclitis with the following typical pathologic features: stromal atrophy, stromal fibrosis, no stromal melanocytes, depigmentation of the posterior pigment epithelium, and infiltrating mononuclear cells (chiefly lymphocytes and plasma cells) in the stroma and anterior border layer (hematoxylin and eosin, $\times 250$).

plexes bind to a structure expressed on the membrane of the iris vascular endothelial cells, such as the receptor for the first complement subcomponent (C1q) described by Daha and associates²⁷ on cultured human umbilical vein endothelial cells.

Recent investigations of systemic vasculitis focused on the presence of antiendothelial cell autoantibodies. Sera from patients with systemic lupus erythematosus contained complement-fixing antibodies and immune complexes that could bind themselves to cultured human umbilical vein endothelial cells.²⁸ Antiendothelial cell antibodies have also been found in 70% of patients with rheumatoid arthritis and vasculitis and in children with active Kawasaki syndrome, a diffuse vasculitis.²⁹⁻³¹ These antiendothelial cell antibodies lyse cultured vascular endothelial cells only when these cells have been exposed previously to gamma interferon, interleukin-1, or tumor necrosis factor. These inflammatory mediators probably induce certain target antigens on the endothelial cells.³¹ The presence of two cytokines, interleukin-2, and gamma interferon, was recently demonstrated in the eyes of patients with uveitis.^{32,33} High concentrations of the cytokine Il-6 have been found in the aqueous humor of patients with Fuchs' heterochromic iridocyclitis.³⁴ Therefore, it would be interesting to investigate whether antiendothelial cell antibodies are present in the serum and aqueous humor of patients with Fuchs' heterochromic iridocyclitis.

Recent studies indicated that human vascular endothelial cells synthesize and secrete complement factors. Both activators (C3) and inhibitors (factor H) are produced and their production is regulated by cytokines (interleukin-1, gamma-interferon).^{35,36} Therefore, the deposits of C3 we observed in the walls of the iris vessels may have either originated from the circulation, or resulted from local (de novo) synthesis by the activated endothelial cells of the iris vessels.

Although earlier iris fluorescein angiographic studies of Fuchs' heterochromic iridocyclitis clearly demonstrated leakage from the iris vessels,^{7,8} we found no light-microscopic evidence of a vasculitic process. The hyalinization of iris vessel walls we found in all our patients with Fuchs' heterochromic iridocyclitis or uveitis was also seen to some degree in the irises of patients with glaucoma and may not have been an abnormal finding.²¹ Immunoglobulin deposition in vessel walls is known to

be associated with several autoimmune disorders, but it is not clear with light microscopy what these deposits mean in the absence of an inflammatory vascular process. In a recent study on temporal arteritis, it was suggested that positive direct immunofluorescence microscopy on temporal artery biopsies with negative light microscopy identifies subclinical temporal arteritis.³⁷ In Henoch-Schönlein purpura, a systemic IgA-mediated immune complex vasculitis, IgA was found in the vessel walls of 78% of the normal-appearing skin biopsy specimens.³⁸

No specific immune deposits could be identified in the irises of patients with Fuchs' heterochromic iridocyclitis as compared with the findings in irises of other patients with uveitis. A recent analysis of iris biopsy specimens also failed to show any specific immunohistologic abnormalities in Fuchs' heterochromic iridocyclitis as compared with the findings in other uveitis entities.²¹ Therefore, although Fuchs' heterochromic iridocyclitis may be a single clinical entity, it may not be caused by one specific (immuno) pathogenic mechanism.

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