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CLINICAL ASPECTS AND ETIOLOGY OF FUCHS' HETEROCHROMIC CYCLITIS

(KLINISCHE ASPECTEN EN ETIOLOGIE VAN DE HETEROCHROME CYCLITIS VAN FUCHS)

proefschrift

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Chapter 1

GENERAL INTRODUCTION

Fuchs' heterochromic cyclitis is characterized by a chronic, low-grade non-granulomatous anterior uveitis with widely scattered small keratic precipitates, a variable degree of atrophy and depigmentation of the iris, and no synechiae. It is usually unilateral, although bilateral involvement has been reported in up to 10 % of cases. Fuchs' heterochromic cyclitis occurs in approximately 5 % of all patients with uveitis and is regarded as a distinct nosological entity. The typical age of onset is in the third or fourth decade, and there is an equal incidence among men and women. Because not all characteristic clinical signs are present at the same time, the diagnosis of Fuchs' heterochromic cyclitis is often difficult to make, especially in the earlier stages of the disease. No minimal clinical diagnostic criteria, pathognomonic for this eye disease, have been internationally accepted yet, and no laboratory tests are available to confirm the diagnosis of Fuchs' heterochromic cyclitis. Fuchs' heterochromic cyclitis may even be considered as the most commonly misdiagnosed form of uveitis.

Cataract and glaucoma are two major complications in Fuchs' heterochromic cyclitis. A subcapsular cataract develops in almost all cases, whereas glaucoma occurs in approximately 20 % of the cases. Cataract extractions with or without intraocular lens implantation currently have excellent results. Glaucoma is considered to be the most serious complication, because the therapy of glaucoma (medical and surgical), as reported in the literature, has a poor outcome.

The origin of Fuchs' heterochromic cyclitis is still unknown and many hypotheses for the etiology of this eye disease have been proposed since Ernst Fuchs presented his theory in 1906. In chronological order, these theories are the following: Sympathetic Theory, Hereditary Theory, Association with Toxoplasmosis, Vascular Theory and Immunologic Theory. Until now, no definite proof has been obtained to accept or to reject any of these theories.

AIM OF THE THESIS

The aim of this thesis was to study the clinical aspects and etiology of Fuchs' heterochromic cyclitis. An update of the literature on Fuchs' heterochromic cyclitis is presented in chapter 2.

Clinical Aspects

Based on an analysis of clinical findings in 51 patients, clinical diagnostic criteria for Fuchs' heterochromic cyclitis are proposed in chapter 3. In chapter 4, the severity and prognosis of secondary glaucoma are evaluated, based on a larger series of patients with Fuchs' heterochromic cyclitis who needed medical and surgical intervention for glaucoma. Iris

translucency, an important clinical feature, is quantified in patients with Fuchs' heterochromic cyclitis by a modification of the direct compensation technique for the measurement of intraocular stray light in chapter 5.

Etiology

Different approaches have been used to study the various etiological theories on Fuchs' heterochromic cyclitis. One case report and a short review of the literature to support the sympathetic theory and the association between Fuchs' heterochromic cyclitis and the Parry Romberg syndrome are presented in chapter 6. Two cases with Fuchs' heterochromic cyclitis and a definite (congenital) ocular toxoplasmosis (chapter 7 and 8), and clinical and laboratory examinations for ocular toxoplasmosis in a larger series of patients with Fuchs' heterochromic cyclitis (chapter 9) are reported to elucidate the association between Fuchs' heterochromic cyclitis and toxoplasmosis-like chorioretinal lesions. The alternative hypothesis for the chorioretinal lesions in Fuchs' heterochromic cyclitis, namely that of autoimmunity directed against retinal antigens, was evaluated in chapter 10. Chapter 11 describes the detection of circulating autoantibodies against the anterior segment (uvea, cornea) of the eye in patients with Fuchs' heterochromic cyclitis. In chapter 12 the hypothesis of an immune complex vasculitis of the iris vessels was assessed with an immunofluorescence technique on peripheral iridectomies of patients with Fuchs' heterochromic cyclitis.

Chapter 2

FUCHS' HETEROCHROMIC CYCLITIS: REVIEW OF THE LITERATURE

Historical Background

Fuchs' heterochromic cyclitis is a unique disease entity in many of its clinical aspects. In 1906, Ernst Fuchs (Fig. 1) presented a detailed description of 38 patients with heterochromic cyclitis, which he had closely examined in the preceding 10 to 15 years.[1] He combined the presentation of his clinical findings with histopathologic studies on post-mortem or post-enucleation eyes from six of his patients. His clinical descriptions were very accurate and complete and little was left to add by later authors. Although his classical paper appeared in 1906, Fuchs was not the first author to observe this disease. He referred in his original manuscript to seven cases described by Weil in 1904.[2] Furthermore, Bistis[3] had published a report of a similar symptom complex in 1898, although it is doubtful whether he recognized its inflammatory nature.[4] Still earlier, the coincidence of heterochromia and cataract was recognized by Lawrence in 1843, and a scientific report on this subject was published by Hutchinson in 1869.[5]

Terminology and Classification

Any inflammation of the uveal tract, which comprises the iris, ciliary body or choroid is called uveitis.[6] Usually, the inflammation is not confined to one of these intraocular structures. Adjacent tissues, including the retina, vitreous, and optic nerve are affected simultaneously.[6,7] Therefore, these structures are also incorporated in the terminology of uveitis: inflammation of the iris and ciliary body is called iridocyclitis and inflammation of the retina and choroid is called retinochoroiditis or chorioretinitis.[6,7] Because the etiology of uveitis remains frequently unknown, the International Uveitis Study Group (IUSG) has introduced a classification system based on the anatomical localization of the intraocular inflammation: anterior uveitis (iris and ciliary body), posterior uveitis (choroid, often including the retina), intermediate uveitis (peripheral retina and pars plana of ciliary body), or panuveitis (generalized inflammation of the whole uvea).[8,9]

For Fuchs' heterochromic cyclitis this descriptive anatomical classification system by the IUSG is more appropriate than a classification system based on the etiology, since the cause of this eye disease is still unknown. Fuchs' heterochromic cyclitis is often classified as an anterior uveitis. However, when many vitreous opacities or even chorioretinal lesions are present it is better to categorize this eye disease as a panuveitis. By the guidelines of the IUSG[8], the clinical picture of Fuchs' heterochromic cyclitis may be summarized as follows: a chronic, mostly unilateral non-granulomatous disease, involving mainly the anterior uvea, insidious in onset, low-grade in activity, affecting both sexes equally, with a preponderance in the age group

between 20 to 45 years, responding poorly to corticosteroid therapy, without systemic disorders, and generally retaining good vision, except for the development of cataract and glaucoma.

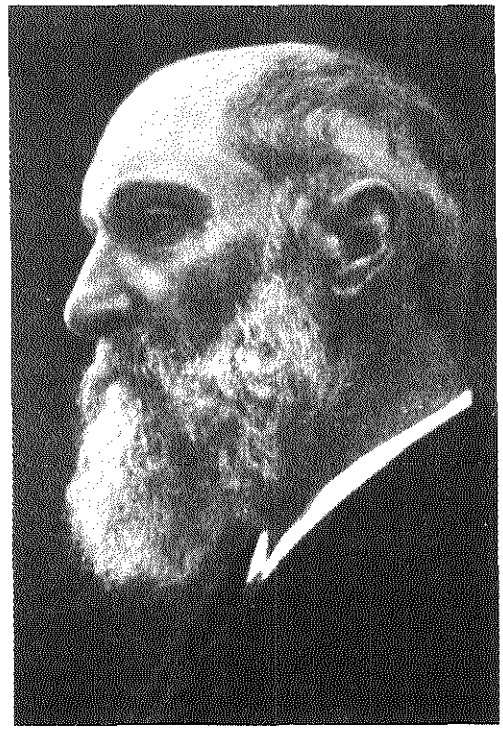

Fig. 1- Ernst Fuchs, Professor of Ophthalmology at the University of Vienna. (Reprinted from Duke-Elder, System of Ophthalmology, vol.II)

Epidemiology

The prevalence of uveitis in a general population has been reported by Vadot et al.[10] based on a prospective epidemiological survey in the Savoy (France) : 38 cases of uveitis per 100.000 residents, with an annual incidence of 17 per 100.000. A similar annual incidence was also found in other West-European countries (Denmark, England).[11,12] The age at which Fuchs' heterochromic cyclitis is most commonly discovered is between 20 and 50 years, and anterior uveitis was the type of uveitis seen most often.[13] The prevalence of Fuchs' heterochromic cyclitis in the above mentioned survey was 1.8 per 100.000 residents.[10]

In other parts of the world, the prevalence and incidence of uveitis differs from the figures in West-Europe and within the uveitis population other uveitis entities prevail.[13] Moreover, Henderly et al.[14] have found that the differential diagnosis of uveitis has changed throughout time because new clinical entities have been described, and improved diagnostic techniques have become available. Differences in prevalences between studies may also be attributed to a different selection of patients.

In the Netherlands, Fuchs' heterochromic cyclitis was found in 5 to 10 % of all cases with uveitis.[9,13,15] This prevalence was similar to that reported by Perkins and Folk[16] in a uveitis population from London and Iowa. Other studies on patients with uveitis however, reported a prevalence of approximately 2 % (Southern California, Israel).[14,17,18] Most of these clinical (that is not epidemiological) studies are based on a caucasian uveitis population and little is known about the prevalence of Fuchs' heterochromic cyclitis in non-caucasians.

Clinical Features

Many reports have been published on heterochromic cyclitis, since Ernst Fuchs first described this disease in 1906.[1] The main purpose of these studies was to elucidate the etiology of Fuchs' heterochromic cyclitis, which is still unknown. In addition to the original description of Fuchs himself, many authors used the classical triad of signs, first described by Kimura, Hogan and Thygeson in 1955,[18] as a basis on which Fuchs' heterochromic cyclitis patients were selected. This classical triad consists of heterochromia, a mild chronic cyclitis and cataract.

The diagnosis of Fuchs' heterochromic cyclitis however, is often difficult to make because the distinct clinical signs are not always present at the same time. Results of studies on the etiology may not be compared, if authors use different diagnostic criteria. Moreover, for the patient with Fuchs' heterochromic cyclitis it is important that the disease is recognized, because incorrect diagnosis may lead to unnecessary therapy (corticosteroids, cycloplegics) and failure to detect secondary glaucoma.

No minimal clinical criteria for establishing the diagnosis of Fuchs' heterochromic cyclitis have been internationally accepted yet. By means of clinical analyses of patients with Fuchs' heterochromic cyclitis in different parts of the world, predominant clinical findings may be distinguished and combined to form internationally accepted clinical diagnostic criteria. This is important, since no diagnostic laboratory test(s) are yet available to confirm the clinical diagnosis of Fuchs' heterochromic cyclitis. Recently, La Hey et al.[19] proposed diagnostic criteria

for this eye disease on the basis of a clinical analysis of 51 patients with Fuchs' heterochromic cyclitis in the Netherlands (Table 1). These criteria still need to be confirmed by analyzing other forms of uveitis, which are difficult to differentiate from Fuchs' heterochromic cyclitis (Posner-Schlossman Syndrome, intermediate uveitis, sarcoidosis) and by investigating patients with Fuchs' heterochromic cyclitis in other countries, especially in a non-caucasian population.

Table 1- Diagnostic criteria for Fuchs' heterochromic cyclitis based on the major clinical findings.[19]

I. Essential features*	II. Associated features†
- Absence of acute signs (severe redness, pain and photophobia)	- Unilaterality of the uveitis - Heterochromia
- Characteristic keratic precipitates and/or minimal cells and flare in the aqueous (1+ or 2+)	- IPE atrophy - Subcapsular cataract - Elevated intraocular pressure
- Diffuse iris stromal atrophy	- Vitreous opacities
- Absence of synechiae	- Chorioretinal lesions

IPE = Iris posterior pigment epithelium * All must be present † At least two must be present.

For the purpose of this thesis, Fuchs' heterochromic cyclitis was defined as a disorder with the following **essential features** (obligatory signs) and **associated features** (facultative signs):

Essential Features

Absence of acute signs

Patients with Fuchs' heterochromic cyclitis have no signs of frank inflammation: they show no miosis or ciliary injection, and experience no symptoms of severe pain or photophobia.[5] They often present with a "quiet white eye".[18] Usually, patients with Fuchs' heterochromic cyclitis are unaware of their disease, until vision decreases because of cataract or vitreous floaters.[6]

Characteristic keratic precipitates

Precipitates on the posterior corneal surface are almost a constant sign in this disease.[18] These keratic precipitates are small, may be round or star-shaped,[20] and are white or translucent. Their number is variable. Characteristically, they may be scattered over the whole corneal endothelium.[20] These precipitates reappear after some days, weeks, or even years[20] on the endothelium after cataract extractions, and they are composed of lymphocytes.[21] Fine filaments are generally found between these precipitates.[21]

Minimal cells and flare in the aqueous

In the aqueous humor, often no or only a minimal Tyndall phenomenon (flare) is visible, whereas circulating cells are more frequently found.[18,20]

Iris stromal atrophy

Atrophy and depigmentation of the stroma and anterior border layer of the iris are a predominant finding in Fuchs' heterochromic cyclitis. It is mainly the depigmentation of the anterior border layer of the iris that causes the heterochromia.[22] The iris atrophy is diffuse in character and the presence of sectorial iris atrophy strongly suggests a different diagnosis.[22] The entire iris in Fuchs' heterochromic cyclitis has a peculiar appearance: it looks dull and flat; the iris relief and crypts are less clearly marked than in the normal eye.[5] Probably due to the atrophy of the iris, radial iris vessels seem more prominent and sometimes even rubeosis may be seen.[23] In a recent study, the atrophy and depigmentation in patients with Fuchs' heterochromic cyclitis was quantified, and it was found that this process not only occurs in the iris, but also in the ciliary body.[24]

Absence of posterior synechiae

Normally no posterior synechiae are found in patients with Fuchs' heterochromic cyclitis. According to Kimura, Hogan and Thygeson[18] they may, however, occasionally be seen when Fuchs' heterochromic cyclitis is complicated by glaucoma.

Associated Features

Unilateral ocular involvement

In almost 90 % of the patients with Fuchs' heterochromic cyclitis only one eye is affected; bilateral involvement has been reported to occur in 8 to 12 % of the cases.[5,21]

Heterochromia

Two forms of heterochromia (i.e. alterations in iris pigmentation) may be distinguished: heterochromia iridis or iris bicolor (a colour difference within a single iris), and heterochromia iridum which is also known as a colour difference between the two eyes of an individual.[25] Heterochromia was already known to the ancients: Aristotle described heterochromia in humans and horses, and both Alexander the Great and his horse Bukephalos were said to have one light and one darker eye.[5] Heterochromia in general, may be congenital or acquired (Table 2). Anomalies which may be associated with heterochromia are presented in Table 3.[26]

Table 2- Major causes of iris heterochromia

Congenital
Genetic (autosomal dominant trait, sporadic, familial)
Prenatal toxic or other noxious influences
Waardenburg syndrome
Chediak-Higashi syndrome
Parry-Romberg syndrome (hemifacial atrophy)
Tuberous sclerosis
Iris naevus
Iris melanocytosis
Acquired
Hyperchromic heterochromia
Naevus of the iris
Malignant melanoma of the iris
Melanosis bulbi (excessive pigment in all pigmented layers of the eye)
Trauma (perforating injuries or contusions of the eye)
Metallic siderosis (rusty colour due to intraocular iron fragments)
Iris abcess
Neurofibromatosis
Neovascularization (rubeosis iridis)
Hypochromic heterochromia
Idiopathic or secondary iris atrophy
Horner's syndrome
Iridocyclitis due to localized or systemic diseases such as syphilis, tuberculosis, rheumatoid arthritis, herpes zoster, herpes simplex, anaemia, or ocular leprosy
Diabetic rubeosis iridis
Ischemic neovascularization
Posner-Schlossman syndrome
Association with iris coloboma

Although it is a characteristic feature, the heterochromia in Fuchs' heterochromic cyclitis, which is a heterochromia iridum, is not always present.[18,20] Heterochromia may be difficult to recognize in case of dark-brown- or light-blue irides,[18,22,27,28] in case of inverse heterochromia,[20] and especially in the early stages of the disease.[5] Inverse heterochromia, indicating that the darker eye is the affected eye, sometimes occurs in patients with blue eyes: progressive atrophy of a light-blue iris stroma will reveal the dark posterior pigment epithelium and cause an apparent deepening of the blue colour.[18,22] In black patients, heterochromia may frequently be absent.[27,28]

Fuchs reported that the heterochromia usually had been present since early childhood.[1] In 11 to 15 % heterochromia may be congenital[20,23] but often patients note their heterochromia a few years before the other signs of Fuchs' heterochromic cyclitis appear, and some patients notice it only when their vision decreases.[5]

Transillumination defects of the iris

Due to focal atrophy and depigmentation of the posterior epithelial layer of the iris, this pigmented layer often has a "moth-eaten" appearance. Transillumination through the pupil may demonstrate these areas of atrophy of the pigmented epithelium, particularly around the pupillary margin.[29] Often these defects in the posterior iris layer develop later in the disease process than the atrophy of the other iris layers.[22]

Iris nodules

Small, greyish nodules may be found at the pupillary margin of the iris (Koeppe nodules).[20] Larger nodules may be found on the anterior surface of the iris, especially in the sphincter area: these are called Busacca nodules. Exceptionally, these Busacca nodules may be found spread over the whole iris surface.[20] Fine drawings of these nodules were published in 1942 by Vogt.[30] In black patients with Fuchs' heterochromic cyclitis, the presence of these iris nodules, coupled with subtle or absent heterochromia, may often mislead ophthalmologists to diagnose the case as a chronic granulomatous iridocyclitis.[27] The fact that these iris nodules do not lead to synechiae formation is in such cases helpful in establishing the diagnosis of Fuchs' heterochromic cyclitis.[27]

Iris crystals

The presence of multiple small white-yellowish iris crystals has been reported in two patients with Fuchs' heterochromic cyclitis.[31,32] They probably represent Russell bodies (globular plasma cell inclusions, consisting of compact, homogeneous aggregates of immunoglobulins)[1,4] and may be associated with hypergammaglobulinemia. In one patient, they reappeared three months after cataract extraction on the same location.[32]

Increased fluorescein permeability of the blood-aqueous barrier

In 1946, Amsler devised a method to test the permeability of the blood-aqueous barrier.[33] After an intravenous injection of fluorescein, a time-plot (curve) was constructed of its appearance in the aqueous fluid.[33] In normal eyes, not much fluorescein penetrated into the aqueous. In eyes with uveitis, glaucoma or trauma, a peak of fluorescein became visible

Table 3- Anomalies which may be associated with heterochromia[26]

Skeletal anomalies	**Cutaneous anomalies**
Asymmetrical skull	Romberg's facial hemiatrophy
Facial asymmetries	Partial albinism
Mandibulofacial dysostosis	Sturge-Weber syndrome
Cleft palate and harelip	Scleroderma en coup de sabre
Hypertelorism	Unilateral facial anhidrosis
High arched palate	Peutz-Jegher-Tourraine syndrome
Spina bifida	Xanthomatosis
Kyphosis	Acrocyanosis
Scoliosis	Naevus of Ota
Sprengel's shoulder	Auricular appendages
Cervical rib	Vascular naevi
Klippel-Feil anomaly	Ectodermal dysplasia
Funnel chest	Neurofibromatosis
Winged scapula	
Spondylolisthesis	**Neurological abnormalities**
Abnormally long arms	Agenesis of corpus callosum
Arachnodactyly (spider fingers)	Meningeal hemiangiomata
Crooked little fingers	Congenital third nerve palsy
Club foot	Congenital sixth nerve palsy
Nail-patella syndrome	Congenital seventh nerve palsy
Webbed fingers	Moebius syndrome (congenital sixth and seventh cranial nerve paralysis)
Soft tissue anomalies	Waardenburg's syndrome
Abnormally shaped ears	Hydromyelia
Bifid uvula	Syringomyelia
Cervical fistula	Klumpke's paralysis
Hypoplasia of the ipsilateral breast	Barre-Lieou syndrome
Hypopigmentation of the ipsilateral nipple	Tuberous sclerosis

Ocular abnormalities

Idiopathic or secondary iris atrophy
Genetic heterochromia (autosomal dominant trait, sporadic, familial)
Iris coloboma
Iris naevus
Iris melanocytosis
Malignant melanoma of the iris
Melanosis bulbi (excessive pigment in all layers of the eye)
Iris trauma (perforating injuries or contusions of the eye)
Metallic siderosis (rusty colour due to intraocular iron fragments)
Iris neovascularization
Iris hyperaemia
Iris haemangioma
Iris abcess
Iris vitiligo
Axenfeld's syndrome and Rieger'anomaly (mesodermal dysplasia of the anterior segment)
Microcornea
Macrocornea
Fuchs' heterochromic cyclitis
Iridocyclitis due to localized or systemic diseases such as syphilis, tuberculosis, rheumatoid arthritis, herpes zoster, herpes simplex, ocular leprosy or anaemia
Posner-Schlossman's syndrome
Georgiades syndrome (iris hypoplasia with cataract)
Maculopathy
Foveal dystrophy
Juvenile macular degeneration
Chorioretinal dystrophy
Retinitis pigmentosa
Rubella syndrome
Micropthalmia
Unilateral myopia
Unilateral myopic astigmatism
Horner's syndrome

Gastrointestinal anomalies

Enterogeneous cysts of the gastrointestinal tract

Miscellaneous

Marfan's syndrome
Subclavian steal syndrome
Hallerman-Streiff syndrome
Vogt-Koyanagi-Harada-syndrome
Somatic mosaicism
Polycythemia rubra vera
Chediak-Higashi-syndrome

much sooner after the injection than in normal eyes. The curves of the eyes of patients with Fuchs' heterochromic cyclitis however, showed the most severe leakage.[33] Later, this striking increased permeability of the blood-aqueous barrier was also found in fluorescein angiographic studies of the iris[34-36] and in a study on aqueous humor dynamics by Johnson et al.[37] No control eyes of other types of uveitis were, however, included in these latter studies.

Fluorescein angiographic studies of the iris

Simultaneous bilateral fluorescein angiographic studies of the iris, performed in patients with Fuchs' heterochromic cyclitis, showed profound, mainly peripupillary, fluorescein leakage of the iris vessels in all affected eyes. This fluorescein leakage was most prominent at the site of the new-formed vessels, but was also seen in cases without neovascularization.[34-36] In addition, filling defects and perfusion delays were found, indicating areas of ischemia. These ischemic areas were frequently associated with neovascularization.[34-36] Also in some of the contralateral eyes, minimal fluorescein leakage was found at the pupillary border, but no neovascularization or ischemic sectors could be detected.[34] A later study, which performed iris fluorescein angiographic studies in patients with iris rubeosis due to chronic anterior uveitis of various causes (including two cases of Fuchs' heterochromic cyclitis), showed that the neovascularization in the chamber angle and the irregular superficial leaking iris vessels are not specific for Fuchs' heterochromic cyclitis.[38]

Chamber angle

Although a normal open angle is often found in patients with Fuchs' heterochromic cyclitis, gonioscopic examinations have shown increased numbers of abnormal blood vessels near the chamber angle in these patients.[4,5] These abnormal vessels appeared as newly-formed vessels, and because they were more fragile than normal vessels, they were thought to cause Amsler's filiform haemorrhage.[4,5] The increased angle vasculature is however, not a constant finding in Fuchs' heterochromic cyclitis, and may also be found in other diseases.[4,5,38] Furthermore, it is not certain whether these angle vessels are really pathological, since Henkind also found numerous fine vessels in the anterior chamber angle of more than one-third of the 269 normal eyes he examined.[39] Their frequency appeared to be correlated with the degree of pigmentation of the eye. It is therefore possible that the apparent increase of angle vessels in the light eye of patients with Fuchs' heterochromic cyclitis, is the result of a greater visibility of such vessels, due to depigmentation of the anterior iris stroma near the chamber angle.[5]

Sometimes, small scattered peripheral anterior synechiae are found in the chamber angle of patients with Fuchs' heterochromic cyclitis (appearing also in non-operated eyes).[23] Undifferentiated tissue or hyaline membranes have also been found,[5,20,23] but no abnormal pigmentation or exudates have been detected in the chamber angle of patients with Fuchs'

heterochromic cyclitis.[5] The presence of abnormal findings in the chamber angle does not correlate with the incidence and severity of glaucoma.[23,27]

Filiform Haemorrhage (Amsler's sign)

A characteristic filiform haemorrhage, which is also known as Amsler's sign, develops after paracentesis in the anterior chamber angle, opposite to the point of puncture.[4,40] Later, it was observed that this bleeding also occurred on the peripheral anterior iris surface.[5] Amsler and Verrey were the first to describe this phenomenon, which occurred in 22 of their 23 patients with Fuchs' heterochromic cyclitis.[40] In patients in whom the puncture was repeated, the haemorrhage appeared again in exactly the same way: but it never occurred in the normal opposite eyes of these patients, nor in the eyes of patients with simple hereditary heterochromia or with sympathetic heterochromia.[5,40] In other forms of uveitis, after tapping of the anterior chamber, such haemorrhages were rare, and if they appeared they looked different: diffuse, blood mixed with the aqueous, and the bleeding did not run in a discrete fine filament to collect in a small hyphema at the bottom of the anterior chamber as in Fuchs' heterochromic cyclitis.[40] Amsler and Verrey concluded that this filiform haemorrhage was pathognomonic for Fuchs' heterochromic cyclitis. Probably sudden changes in the anterior chamber pressure during puncture caused the rupture of fragile (or abnormal) vessels near the chamber angle.[40]

Later, another mechanism was proposed for this typical hyphema: the haemorrhage originated from the canal of Schlemm and could be evoked by gonioscopy.[41] From the canal of Schlemm it would leak into the trabeculae and subsequently emerge into the anterior chamber. This "goniohemorrhage" occurred in 100 % of the affected eyes, but also in 70 % of the non-affected eyes of the patients with Fuchs' heterochromic cyclitis. In none of the control eyes with iris atrophy due to other causes (chronic simple glaucoma, diabetes, chronic uveitis, or Horner's syndrome) such a goniohemorrhage could be elicited.[41]

Today, the Amsler's sign is still used as a diagnostic marker for Fuchs' heterochromic cyclitis by some European ophthalmologists.[4] It is however, not clear whether the Amsler's sign is a true pathognomonic sign, since in 75 cases examined by two IUSG members, it was not found in all patients with Fuchs' heterochromic cyclitis,[21] and has also been reported in other types of uveitis.[6,21] Moreover, it is no longer accepted to perform an anterior chamber tap solely for the purpose of observing the haemorrhage.[6]

Pupil

The pupil in the eyes of patients with Fuchs' heterochromic cyclitis may be enlarged or irregular, and it may react poorly to light stimulation or near vision.[4,5] This mydriasis and slow contractions are probably due to the fact that the sphincter muscle is also involved in the process of atrophy of the iris.[4,5]

Subcapsular cataract

Early in the disease the lens is clear. The cataract, which is of a complicated type that starts in the posterior cortex beneath the capsule, develops in almost all cases, and is the result of a long-standing cyclitis.[21] This late development limits the value of cataract as diagnostic sign.[18] The subcapsular cataract in Fuchs' heterochromic cyclitis does not differ in appearance from that developing in other forms of chronic uveitis.[4]

Vitreous Opacities

Scattered fine and coarse opacities are often present in the vitreous of these patients. In contrast to uveitis of any other etiology, these opacities are nearly exclusively white and not brownish.[20] In addition to cells and white dots, curtain-like membranes, forming more or less compact veils may frequently be seen.[20]

Chorioretinal Lesions

Fuchs' already noted chorioretinal lesions in three of the 38 patients with heterochromic cyclitis.[1] In two of his patients these were active foci of chorioiditis, and in one patient he observed atrophic choroidal lesions in the affected, but also in the non-affected eye. In 1955, Franceschetti reported that these chorioretinal alterations in Fuchs' heterochromic cyclitis were exceptional and more often of the degenerative than of the inflammatory type.[20] One has to realise, however, that it is not possible to make such a distinction on the basis of a chorioretinal scar. Kimura believed that although peripheral chorioiditis is occasionally observed in these patients, it is often missed because the peripheral retina is rarely examined.[18]

Elevated Intraocular Pressure

Any inflammation involving the ciliary body may suppress its function, leading to a lesser production of aqueous humor, and thereby a normal or hypotensive intraocular pressure.[6] This may happen at first in patients with Fuchs' heterochromic cyclitis, but if the inflammation becomes chronic, the trabecular outflow system may become embarrassed due to aqueous protein[1] and/or inflammatory damage to the trabeculum, and intraocular pressure may start to rise.

Fuchs[1] found an increased intraocular pressure in three of his 38 patients with heterochromic cyclitis and thought that the glaucoma was caused by a high outflow resistance due to increased proteins in the aqueous humor. Hart showed in a study on the aqueous dynamics in patients with Fuchs' heterochromic cyclitis, that not only the affected eyes, but also 10 of the 16 uninvolved contralateral eyes had a reduced outflow value.[42,43] Huber[44,45] and later Velicky[46] reported that after anterior chamber paracentesis sometimes an acute intraocular pressure rise occurred, and suggested that this could be used as a provocative test for glaucoma in Fuchs' heterochromic cyclitis.

In approximately 12 to 25 %, Fuchs' heterochromic cyclitis may be complicated by a progressive glaucoma that threatens the vision of the patient.[42-50] In contrast with cataract, treatment (medication or surgery) of secondary glaucoma, as reported in the earlier literature[23,48-50] has no favourable results (success 0 to 57 %). In a more recent study, surgical intervention (mostly trabeculectomies) with modern techniques (use of fibrosis inhibitors and sodium hyaluronate) yielded successful control of intraocular pressure in 72 % of the 18 operated patients.[51]

The pathogenesis of glaucoma in Fuchs' heterochromic cyclitis is still poorly understood. In the majority of cases it is an open angle glaucoma.[4] Light and electron microscopic studies on the trabecular meshwork in these patients are scarce and controversial. Huber et al.[44,45] demonstrated an increased outflow resistance with sclerosis of the trabecular meshwork in Fuchs' heterochromic cyclitis, while Benedikt et al.[52] noted atrophy of the wall and a collapse of the canal of Schlemm. Clinical findings include neovascularization of the chamber angle,[53,54] anterior synechiae,[55] phacolytic glaucoma,[56,57] trabeculitis,[4,54,58] and steroid induced glaucoma.[50,59]

Specular Microscopy: Corneal Endothelial Cells

Quantitative analysis of corneal endothelial cells in 14 patients with Fuchs' heterochromic cyclitis by Saari et al.,[60,61] showed no statistically significant differences in endothelial cell densities, mean cell area, coefficient of variation of cell area (a measure of cellular polymegathism), mean cell perimeter, and mean number of apices of the endothelial cells (a measure of cellular pleomorphism), when affected eyes were compared with their healthy fellow eyes. The cell density was 5 % lower in the (non-operated) eyes with Fuchs' heterochromic cyclitis than in the unaffected eyes. Marked losses in endothelial cell count (up to 50 %) however, were found in two eyes with Fuchs' heterochromic cyclitis that had undergone an intracapsular cataract extraction and in one eye with glaucoma. Thus, it was suggested that, although Fuchs' heterochromic cyclitis does not seem to accelerate the age-related endothelial cell reduction, there may be an altered tolerance against endothelial traumas in this disease.[60,61] Further studies, in which normal eyes with previous cataract extractions operated by the same surgeon are included as controls, are however, necessary to confirm this suggestion.

The previously mentioned results are different from those reported by Brooks et al.,[62-64] who studied a group of 30 patients with Fuchs' heterochromic cyclitis, including some cases with glaucoma, and a few patients who underwent previous cataract surgery. These authors showed marked changes in endothelial cell count and altered cellular morphology, especially in older patients with Fuchs' heterochromic cyclitis and in patients with secondary glaucoma. They compared results in patients with Fuchs' heterochromic cyclitis with results in other types of chronic uveitis, pseudoexfoliation syndrome, and pigment dispersion syndrome, and found the most striking changes in endothelial cells in patients with Fuchs' heterochromic cyclitis.[62-64] Factors producing these endothelial changes could be

hypoperfusion of the iris, intercellular oedema (bleb formation) acting over a longer period, and raised intraocular pressure.[62-64]

Typical qualitative changes of the corneal endothelium in the eyes with Fuchs' heterochromic cyclitis were found in all studies mentioned above: intra-and intercellular dark bodies, larger dark defects spanning several endothelial cells, dark non-reflecting areas, and bright irregular patchy areas crossing cell borders.[60-64] It was suggested that the black bodies corresponded with single lymphocytes on the corneal endothelium, that the larger defects covering several endothelial cells corresponded with the keratic precipitates,[61] and that the dark non-reflecting areas may represent subendothelial oedema.[64] The origin of the bright irregular patchy areas is not clear. These qualitative endothelial cell changes are not pathognomonic for Fuchs' heterochromic cyclitis, since they may also be seen in other types of anterior uveitis.[60-64]

Histopathology of the Iris

Normal iris

The normal iris (Figs. 2 and 3) can be divided into the following parts: [25,65,66] (1) an anterior border layer, formed by fibroblast-like cells with dendritic processes, intertwined with the dendritic processes of anterior border melanocytes, (2) a loosely arranged iris stromal layer, containing morphologically identical cells, and the sphincter muscle which lies in the pupillary portion of the iris stroma, (3) the anterior epithelium and dilatator muscle layer, in which each cell is composed of an epithelial apical portion and a muscular basal portion,[65] and (4) the posterior pigment epithelial layer with cuboidal, heavily pigmented, epithelial cells.

The blood vessels in the iris are predominantly capillaries, but also arterioles and venules may be found. The capillaries are formed by a single layer of unfenestrated endothelium with a rather thick basement membrane. Melanocyte processes are frequently seen around the vessels.[65]

The nerves in the iris form fine plexuses along the larger blood vessels, and filaments can be seen in the anterior border layer, in the stroma, and among the muscles, but not in the posterior pigmented epithelium. Most of the nerves are unmyelinated and enclosed by Schwann cells.[65]

The iris melanocytes all contain melanin granules, also known as melanosomes. Melanin is formed in the endoplasmatic reticulum of melanocytes by progressive deposition of pigment, derived from tyrosine, onto a skeleton, also known as premelanosome. All ocular melanogenesis is thought to be completed by the first few months of life.[66] The iris stroma and anterior border layer are of neural crest origin.[67] The posterior iris pigment layer is embryologically similar to the pigmented epithelium of the ciliary body and retinal pigment epithelium, which are derived from the neuroectoderm.[5,65-68] The dilatator and sphincter muscle of the iris are also of neural crest origin.[67]

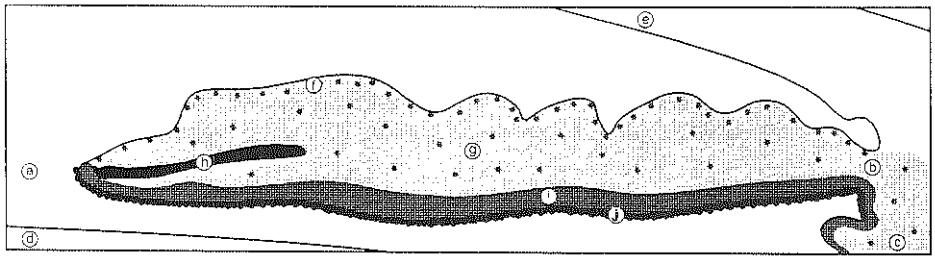

Fig. 2- Normal iris: a pupil, b iris root, c ciliary process, d lens, e cornea, f anterior border layer, g stroma, h sphincter muscle, i anterior epithelial layer of the posterior iris which forms the dilatator muscle, and j posterior epithelial layer.

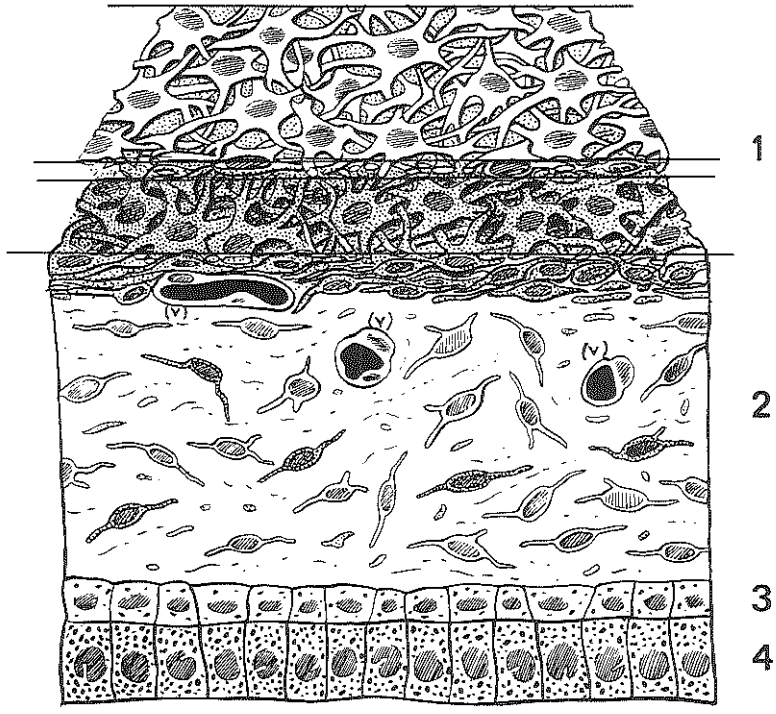

Fig. 3- The normal iris (near the pupillary margin) can be divided into the following parts: [25,65,66] *(1) an anterior border layer, formed by fibroblast-like cells with dendritic processes, intertwined with the dendritic processes of anterior border melanocytes, (2) a loosely arranged iris stromal layer, containing morphologically identical cells and the sphincter, (3) the anterior epithelium and dilatator muscle layer, in which each cell is composed of an epithelial apical portion and a muscular basal portion*[65] *and (4) the posterior pigment epithelial layer with cuboidal heavily pigmented epithelial cells. (v) blood vessel.*

The iris colour is chiefly determined by the presence of anterior border and stromal melanocytes, and the general type of structure of the iris colour is determined genetically.[5] In blue and brown eyes the iris surface is morphologically similar. In darker eyes, the melanocytes of the anterior border layer are heavily pigmented so that they hide the lower iris layers. Therefore, the iris surface looks dark and velvety in brown eyes, while in (light-) blue eyes the relief is marked: through the transparent anterior layer, iris vessels may be observed, and at the bottom of the crypts the black posterior epithelium may be seen.

The Iris in Fuchs' Heterochromic Cyclitis

Light microscopy showed a process of atrophy (and depigmentation) occurring in all layers of the iris and affecting all cell types within these layers (fibroblasts, melanocytes, smooth muscle cells and epithelial cells). A decreased number of melanocytes was found in the anterior border layer and stroma with an abnormal structure: they were abnormally rounded and had lost their dendritic processes. These melanocytes contained relatively few melanin granules, which were smaller than normal and irregular in size and shape.[66,68-71] Also a decreased number of pigment epithelial cells was found, but their melanosomes were not smaller than usual.[66] In addition to stromal atrophy, a diffuse fibrosis of the iris stroma was found, involving the sphincter muscle as well: the entire sphincter muscle could be thin and sclerosed. On the level of electron microscopy, many isolated mitochondria were found in the iris stromal cells (both fibroblasts and melanocytes), suggesting that the process of atrophy destroys the endoplasmatic reticulum first.[71] This phenomenon was also observed, although to a much lesser extent, in control specimens from patients with other types of chronic iridocyclitis.[71]

One must keep in mind that mostly small pieces of iris obtained from only a few patients with Fuchs' heterochromic cyclitis were studied, and that often too much conclusions were based on too little material. Moreover, most histopathologic studies in Fuchs' heterochromic cyclitis were performed on iridectomy specimens, on post-mortem eyes, or on eyes obtained after enucleation, and that no specimens of the opposite normal eye were available for comparison. Any loss of pigmented cells from the iris stroma or pigment epithelium, any thinning or irregularity, may thus also be attributable to artifact or surgical trauma.[70]

Fuchs already described the presence of lymphocytes, plasma cells and Russel bodies in the tissue specimens of the iris.[1,4] These were clearly signs of a chronic inflammation, and Fuchs noted that they were more marked than would be expected on the basis of the clinical picture. Later, light- and electron microscopic studies confirmed his findings.[4,18,55,66-71] Furthermore, occasionally small numbers of mast cells, histiocytes, large mononuclear cells, and eosinophils were found.[29,70,71] In the aqueous humor of patients with Fuchs' heterochromic cyclitis, a similar cell population as in the cellular infiltrates in the iris specimens was observed.[68,70] It was suggested that these cells appeared in the aqueous after

they had been shed from the iris.[70] Similar inflammatory cells were also found in the aqueous humor and iris of patients with other types of chronic iridocyclitis.[70]

Vascular changes were also found in the iris specimens of patients with Fuchs' heterochromic cyclitis: some authors reported abnormal hyalinosis of the vessel wall with narrowing of the vessel lumen,[1,20,29,70] while others could not confirm these findings.[7,55,68,71] In addition, endothelial cell proliferation[1] and thin or irregular vessel walls were found in these iris specimens.[72] Later studies, using control specimens, showed that such hyalinization of the iris vessel walls occurs also in normal irides, and may not be an abnormal finding.[73]

The involvement of nerves in the atrophic process was reported in two studies. One study found a significant reduction of axons and their Schwann cells at the level of the dilatator muscle.[69] A second study reported degenerative changes in most of the non-myelinated (adrenergic) nerve fibers present in the iris.[68]

All above mentioned studies were based on a limited number of small iris specimens and postenucleation or postmortem material from patients with a long lasting cyclitis. Early changes in the disease process were therefore not noted. Only in some studies control specimens from other uveitis entities or normal eyes were included. Until now, it was not possible to differentiate Fuchs' heterochromic cyclitis from other types of chronic iridocyclitis by using histopathological criteria (light- or electron microscopic criteria).

Etiologic Mechanisms

Fuchs' Theory

Fuchs assumed that the syndrome was caused by a noxious factor of unknown origin, which was active from foetal or early post-natal life.[1] First, the normal development of uveal pigmentation would be inhibited, resulting in heterochromia. Later, the eye would respond to this pathologic agent by a low-grade inflammation, which was slowly progressive over many years. This inflammation would cause the fine corneal precipitates, gradually worsen the iris atrophy and often result in vitreous opacities. Cataract was caused by a pathologic alteration of the intraocular fluids, and glaucoma resulted from impaired outflow channels by aqueous protein. Later, many objections were raised against Fuchs' theory: (1) the heterochromia was not always congenital; (2) there were no signs of overt ocular inflammation: no exudates, no synechiae, no ciliary injection, no photophobia, no pain. In fact, it was curious that such a mild cyclitis caused a cataract so often; (3) chronic inflammatory processes are usually bilateral. These objections were repeated many times, were amplified, until it was widely believed that there was no inflammation at all in these eyes.[74]

Sympathetic Theories

The sympathetic theories are based on the fact that sympathetic lesions may be followed by iris hypochromia. It was proposed that the other signs of Fuchs' heterochromic cyclitis were

also caused by a sympathetic defect: poor sympathetic innervation caused vasodilatation with consequent hyperaemia of the ciliary processes and increase in permeability of their capillaries. The composition of the aqueous would be affected, leading to corneal precipitates, vitreous opacities, cataract and sometimes glaucoma. Bistis was the most influential early proponent of the sympathetic theory: he believed that some "trophic" defect in the sympathetic nerve system inhibited the normal process of uveal pigmentation.[75] Experimental evidence for this idea was provided by Bistis by removing the superior cervical ganglion on one side in four rabbits. These rabbits developed heterochromia, and one rabbit also had some aqueous flare, but there were no corneal precipitates or cataract.

Two other conditions have also been associated with Fuchs' heterochromic cyclitis and a sympathetic defect: "status dysraphicus" and progressive facial hemiatrophy (Parry Romberg syndrome). "Status dysraphicus" was introduced by Bremer in 1926.[76] Bremer believed that syringomyelia was due to a faulty closure of the primitive neural tube. He examined relatives of patients with syringomyelia and found that a number of them had "syringomyelia-like-stigmata", which he called "status dysraphicus". Passow[77] diagnosed sympathetic heterochromia in some of Bremers patients, and concluded that Horner's syndrome and Fuchs' heterochromic cyclitis (which he believed was an advanced form of sympathetic heterochromia) were part of this "status dysraphicus". Thus, "status dysraphicus" was believed to be a micro-form of syringomyelia and sometimes Fuchs' heterochromic cyclitis was its sole manifestation.

In addition to stigmata of neuroectodermal tissue, faulty disclosure of the neural tube was also said to cause wide-spread mesodermal defects. Therefore, Marfan syndrome and the Parry Romberg syndrome were also considered to be part of this "status dysraphicus". Other abnormalities frequently reported to be part of "status dysraphicus" were:[20,78,79] (1) skeletal abnormalities, such as kyphoscoliosis, "funnel chest", arm span in excess of height, and short sternum; (2) unilateral conditions, such as Horner's syndrome, pigment asymmetry of the nipples, and facial asymmetry; (3) sensory and motor neuron disturbances, such as acrocyanosis, involvement of the fifth, sixth and seventh cranial nerves.

Parry Romberg is a rare condition, reported by Parry in 1825,[80] and by Romberg in 1946,[81] characterized by a slowly progressive atrophy of the face, primarily involving the skin, subcutaneous fat and muscles. If the bone is also involved, a marked facial deformity may result.[82] In 1964, Sugar and Banks[83,84] reviewed the 13 cases of Fuchs' heterochromic cyclitis associated with facial hemiatrophy reported since 1913, and added another case of their own practice. They suggested that both diseases may result from neurovascular or neurotrophic changes, caused by a disturbance of the sympathetic nervous system.

In 1973, in their extensive review, Loewenfeld and Thompson[74] made the following objections against this sympathetic theory and the association between Fuchs' heterochromic cyclitis,"status dysraphicus" and the Parry Romberg syndrome (facial hemiatrophy): (1) iris hypochromia may result when the sympathetic nerve supply is damaged by birth injuries, for instance by brachial plexus damage, or by forceps delivery. In adults, however, uveal

pigmentation is already completed, and accidental or surgical damage results in a mild change in the colour of the iris only after many years.[74,85] Moreover, after sympathetic denervation, in man and in animals, there is no permanently increased permeability of the blood-aqueous barrier, and the aqueous in such eyes was found to be normal.[74] (2) In a literature review of 1746 cases with Fuchs' heterochromic cyclitis, only 25 cases (1.4 %) with Fuchs' heterochromic cyclitis and Horner's syndrome were found. According to Loewenfeld and Thompson, this is too low an incidence to indicate a relationship between Fuchs' heterochromic cyclitis and the occurrence of a sympathetic defect (Horner's syndrome).[74] They did however, not compare this figure (1.4%) with the product of the prevalences of the separate diseases in the general population, which is necessary when a clinical (epidemiological) association is investigated. (3) Until today, the existence of these "trophic sympathetic nerve fibers" and their localization has not yet been proven, and their mode of action has not been explained. (4) "Status dysraphicus" (including all related physical abnormalities) is a manufactured syndrome without existence in reality. It owes its origin to the imagination of one man and to the uncritical repetition and exaggeration of his words by others. Loewenfeld and Thompson reviewed the cases described by Passow and Bremer extensively, but could not find any constancy in the anatomic findings, nor could they make reasonable correlations between the histopathological changes in the spinal cord, claimed by Bremer and Passow, and the physical appearance of their patients. It seems incredible that this conglomeration of impossibilities has been accepted by so many for such a long time. (5) It is unlikely that facial hemiatrophy is causally related to a sympathetic lesion, since there are many patients with sympathetic lesions without facial hemiatrophy. (6) The majority of descriptions of Fuchs' heterochromic cyclitis found in cases with hemifacial atrophy was not typical: there were unusual (pigmented) keratic precipitates, there was no iris atrophy or heterochromia, and in some cases posterior synechiae were found. Intraocular findings in the Parry Romberg syndrome were more likely part of the inflammatory facial process than due to Fuchs' heterochromic cyclitis.[74]

Despite these arguments put forward by Loewenfeld and Thompson to reject the hypothesis of a (common) sympathetic defect and the association between Fuchs' heterochromic cyclitis and hemifacial atrophy, many authors still support this theory: (1) Since 1973, four more patients with Fuchs' heterochromic cyclitis and the syndrome of Parry-Romberg have been reported.[22,86,87] (2) In 1953 and 1965, two cases were described in which Horner's syndrome and Fuchs' heterochromic cyclitis developed consecutively in the same eye after stellate ganglionectomy.[88,89] Recently, five patients with unilateral Fuchs' heterochromic cyclitis and ipsilateral Horner's syndrome were reported.[50] (3) Pupillary changes, Horner's syndrome and heterochromia are often reported in patients with hemifacial atrophy, and are all signs of an impaired sympathetic nervous system.[90] (4) The vascular leakage seen on the iris fluorescein angiographic studies in Fuchs' heterochromic cyclitis may be caused by a disturbance in the iris vessel innervation, which is solely derived from the sympathetic nerve system.[34-36] (5) Electron microscopic studies in Fuchs' heterochromic

cyclitis have suggested that the hypochromia may result from a defective melanin production, due to abnormal adrenergic innervation.[68] (6) There are more studies pointing to a (common) sympathetic defect involved in the pathogenesis of iris hypochromia, Horner's syndrome, or Parry Romberg syndrome. Laties,[91-93] Ehinger,[94,95] and others[96-98] have demonstrated a direct adrenergic innervation of iris stromal melanocytes. For mammals this is extraordinary, because most melanocytes, for instance those of the skin, have no innervation.[91] In a recent ultrastructural study on rat eyes using anterograde tracing with ^{3}H-leucine (injected into the cervical superior ganglion), definite proof of the presence of numerous sympathetic nerve fibers in the iris stroma was provided.[98] Anterograde tracing with ^{3}H-leucine was used because, in contrast with earlier catecholaminergic fluorescein studies, this gives a 100 % selective labelling of sympathetic nerve fibers. Labelled unmyelinated (without Schwann cell covering) adrenergic nerve terminals were found in close approximation to blood vessels, to smooth muscle cells of the dilatator and the sphincter, and to iris melanocytes. (7) After denervation or decentralization of the sympathetic nervous system on one side in 38 young rabbits, Laties and Lerner[91] noted the occurrence of ptosis, miosis, and a notable discoloration of the iris on the operated side in all rabbits. Moreover, they found a significant decrease in activity of the enzyme tyrosinase in the iris tissue (and choroid) obtained from the ipsilateral side. They suggested that the lightening of iris colour following interruption of the sympathetic pathways to the eye, may be ascribed to inadequate replenishment of melanin within the iris stromal melanocytes. Although at present, there is no direct evidence for melanogenesis or melanin-turnover in iris melanocytes (except for the demonstration of tyrosinase activity)[91,99] recent studies on retinal pigment epithelial cells showed several intermediates and derivatives of melanin biosynthesis.[100] (8) In a recent electron microscopic study[85] of a human iris from a 65-year old patient who had a Horner's syndrome that had existed for at least 40 years, a depletion of anterior border and stromal melanocytes, and an absence of sympathetic (adrenergic) nerve fibers was found. The iris pigment epithelium remained unaffected. It was concluded that postnatal maintenance of iris pigmentation, derived from the neural crest (stroma, anterior border layer) is dependent on an intact sympathetic nerve supply. (9) Evidence for a neurovascular defect involved in the pathogenesis of hemifacial atrophy was found in a recent electron microscopic study on skin biopsy specimens.[82] (10) Moss and Crikelair provided experimental evidence for the sympathetic hypothesis by demonstrating hemifacial atrophy after unilateral cervical sympathectomy in young rats.[101]

The iris hypopigmentation in Fuchs' heterochromic cyclitis and Horner's syndrome may thus be caused by a common end result:[50,68] a defective production of melanin granules due to inadequate function of the adrenergic nerves. Furthermore, defective adrenergic innervation of blood vessels in Fuchs' heterochromic cyclitis, may cause increased permeability of the blood-aqueous barrier with subsequent leaking of proteins, cells and inflammatory mediators into the aqueous.

Hereditary Theory

Because two types of heterochromia are dominantly hereditary, namely "simple" uncomplicated heterochromia and heterochromia in Waardenburg syndrome, it was thought that all types of heterochromia were hereditary.[74] In support of this hypothesis, it was suggested that sympathetic heterochromia was familial and that there were many families with hereditary Fuchs' syndrome, or in which some members had Fuchs' syndrome and others "simple" or sympathetic heterochromia: the three types of heterochromia (i.e. heterochromia in Fuchs' heterochromic cyclitis and Waardenburg's syndrome and "simple" uncomplicated heterochromia) were thus genetically related.[74] Another genetic linkage that was made was that between Fuchs' heterochromic cyclitis and the Parry Romberg syndrome and "status dysraphicus": these diseases were said to have a heredodegenerative nature and the responsible gene had a low penetrance.[74]

The following points must be considered: (1) In Waardenburg syndrome there are other related malformations, the iris is not only pale but also hypoplastic, and the fundus is not normally pigmented.[102] Waardenburg syndrome is not related to sympathetic damage or to Fuchs' heterochromic cyclitis, and it should be considered as a separate syndrome. (2) In 1973, Loewenfeld and Thompson performed an analysis of 1500 cases with Fuchs' heterochromic cyclitis reported in the literature, and found only five families (including one described by Fuchs himself) with two cases of Fuchs' heterochromic cyclitis. No families with three or more cases of Fuchs' heterochromic cyclitis were found.[74] Dernouchamps found six familial cases in the 550 cases with Fuchs' heterochromic cyclitis described by members of the IUSG.[9] The proportion of familial cases is thus very small and does not provide adequate proof for the hereditary theory in Fuchs' heterochromic cyclitis. In addition, Saari found different haplotypes in two cases with Fuchs' heterochromic cyclitis from the same family.[103] (3) The number of families described in the literature with Fuchs' heterochromic cyclitis and Horner's syndrome or with familial occurrence of Parry-Romberg syndrome is very low.[74] (4) In 1956, Makley[72] described an identical twin (monozygotic on the basis of blood grouping and hand-printing), who both developed Fuchs' heterochromic cyclitis when they were 43 years old (one in the right eye, and the other in the left eye). Makley concluded that Fuchs' heterochromic cyclitis was congenital in these twins, but it was not certain whether the cyclitis was hereditary or due to a toxin active during pregnancy, since no other members of the family (parents, other nine children) were (yet) affected.[72] Recently, another pair of monozygotic twins (based on DNA-analysis) was reported, of which only one child had Fuchs' heterochromic cyclitis. According to the author this proves that Fuchs' heterochromic cyclitis has definitely no regular Mendelian inheritance.[104] He suggested because some patients have congenital heterochromia many years before they develop the inflammatory signs of Fuchs' heterochromic cyclitis, that these patients may first have "simple" heterochromia, which is transmitted as a genetic trait, and later, triggered by some second event, the clinical picture of Fuchs' heterochromic cyclitis may develop.[104] (5) Studies on HLA-typing in patients with Fuchs' heterochromic cyclitis have shown no

significant deviation in the distribution of HLA-A or B-antigens in Fuchs' heterochromic cyclitis compared with normal healthy blood donors.[103-106] The frequency of HLA-CW3 and HLA-DRW53 was however, decreased in patients with Fuchs' heterochromic cyclitis compared to healthy controls and a possible role for HLA-linked genetic factors in the pathogenesis was suggested.[106] Further reports with larger series of patients are necessary to confirm this assumption, because studies demonstrating associations between diseases and decreased frequencies of HLA-antigens, are difficult to interpret and require a much larger number of patients.[106]

Association with Ocular Toxoplasmosis

Fuchs already noted the presence of chorioretinal lesions in patients with Fuchs' heterochromic cyclitis. Three theories explaining these fundus lesions in Fuchs' heterochromic cyclitis have thus far been proposed: (I) The fundus lesions are caused by a (previous) Toxoplasma gondii infection.[107] (II) Ocular toxoplasmosis can create a chronic condition that can resemble Fuchs' heterochromic cyclitis, but not have the same pathogenesis.[108] (III) The lesions are of non-toxoplasma origin and may result from autoimmune reactions directed against retinal or choroidal antigens.[109,110]

(I) Until 1982, when de Abreu et al.[107] reported a high incidence (56.5 %) of chorioretinal lesions characteristic of toxoplasmosis in their 23 patients with Fuchs' heterochromic cyclitis, most authors did not associate Fuchs' heterochromic cyclitis with ocular toxoplasmosis. In France in 1985 however, such a high incidence of toxoplasmosis-like lesions was also reported in 17 patients with Fuchs' heterochromic cyclitis.[109] Arffa and Schlaegel in 1984 (n = 67, Indiana, US)[110], Pezzi et al. (n = 119, Italy)[111] and La Hey et al. (n = 88, the Netherlands)[112] also found toxoplasmosis-like lesions in their patients with Fuchs' heterochromic cyclitis, but in a much lower percentage (7.5 to 10 %). Recently Schwab[113] confirmed the earlier studies from Brazil and France: he also reported a high incidence (63 %) of toxoplasmosis-like lesions in his 25 patients with Fuchs' heterochromic cyclitis. Almost 95 % of these toxoplasmosis-like lesions were found in the cyclitic eye, but also some cases with unilateral Fuchs' heterochromic cyclitis and bilateral lesions, and bilateral Fuchs' heterochromic cyclitis with unilateral lesions were found.[107,109-113] Only four patients were described in whom the retinal lesions and Fuchs' heterochromic cyclitis were each unilateral and in opposite eyes.[110,111,113]

Regarding this theory of an association between Fuchs' heterochromic cyclitis and ocular toxoplasmosis, the following points must be considered: (1) Until now, only few patients with Fuchs' heterochromic cyclitis and active toxoplasma retinochoroiditis have been described.[107-109,111,114,115] Recently, a follow-up after 25 years of a patient with a definite bilateral congenital ocular toxoplasmosis, who developed a Fuchs' heterochromic cyclitis in her left eye was reported.[114] In only three cases in the literature,[109,115] the clinical picture of an active Toxoplasma retinochoroiditis was confirmed by aqueous humor analysis: A Goldmann-Witmer coefficient of 5 was found in one case with Fuchs' heterochromic cyclitis

and an active chorioretinal lesion, and a Goldmann-Witmer coefficient of 20 was found in a case with Fuchs' heterochromic cyclitis and a toxoplasmosis-like scar.[109] A third case with Fuchs' heterochromic cyclitis was reported with an active chorioretinal lesion and a positive Goldmann-Witmer coefficient (22) for toxoplasmosis in the contralateral eye.[115] These cases support the association between Fuchs' heterochromic cyclitis and ocular toxoplasmosis (2) The reported prevalence of toxoplasmosis-like lesions in Fuchs' heterochromic cyclitis varies considerably between the studies: 7.5 to 65 %.[107-113] For some part this may be due to the fact that lesions in the peripheral retina are often missed in studies based on retrospective analysis. Furthermore, not all authors used the same criteria and some authors not even mentioned[109] their definition of a "toxoplasmosis-like" chorioretinal scar. Another important explanation may be that the prevalence of Toxoplasma retinochoroiditis differs between populations[14] as evidenced by a difference in prevalence of antibodies against Toxoplasma gondii between various populations.[116-120] Moreover, Toxoplasma gondii strains may vary in their virulence: sometimes the infection is only asymptomatic, and in acute maternal infections in only 33 to 40 % a congenital disease of the newborn results.[121,122] In a recent study, it was shown that of the 28 Toxoplasma gondii strains from a variety of hosts (such as human, cat, goat, chicken) on five continents, only 10 were virulent and had an essential identical genotype.[123] Therefore, it is important that a control group (of other uveitis patients) from the same population and the same location is studied simultaneously. In only four studies control groups of other uveitis patients (HLA-B27 associated anterior uveitis,[110,112] chronic anterior uveitis[111] or patients examined at the retinal clinic[108]) or normal controls from the general population[110] were included. A significantly higher percentage of patients with Fuchs' heterochromic cyclitis had chorioretinal lesions consistent with ocular toxoplasmosis, than these control groups. This finding indicates an association between Fuchs' heterochromic cyclitis and toxoplasmosis-like chorioretinal lesions. The number of patients with Fuchs' heterochromic cyclitis and other non-specific chorioretinal lesions was not significantly different from these control groups. (3) In a recent study,[112] the association between Fuchs' heterochromic cyclitis and toxoplasmosis-like scars could not be substantiated by serological tests for toxoplasmosis (immunofluorescence and ELISA) nor by a test for cellular immunity to Toxoplasma antigen. Analysis of aqueous humor samples for Toxoplasma antibodies also yielded negative results.[112] One must keep in mind however, that no active chorioretinal lesions were present in the patients with Fuchs' heterochromic cyclitis at the time of blood or aqueous humor (during cataract extraction) sampling.[112] Moreover, Toxoplasma serology has no definite diagnostic value for ocular toxoplasmosis, since also in the general population a high prevalence of positive titers exists, mostly due to a past acquired Toxoplasma infection. In addition, even in children with definite ocular toxoplasmosis sometimes a negative Sabin-Feldman dye test was encountered. [122] Thus, on the basis of the previously mentioned studies, a congenital Toxoplasma gondii infection may be responsible for the secondary development of Fuchs' heterochromic cyclitis in a small subset of patients.

(II) Regarding the second theory about the fundus lesions in Fuchs' heterochromic cyclitis; Schwab[108] recently reported that in five of his 16 patients with Fuchs' heterochromic cyclitis and toxoplasmosis-like lesions the typical corneal precipitates were absent. Moreover, as has been observed earlier,[111] patients with ocular toxoplasmosis sometimes have clinical findings closely resembling those of Fuchs' heterochromic cyclitis.[108] Schwab therefore suggested that ocular toxoplasmosis can create a chronic condition that can resemble Fuchs' heterochromic cyclitis, but not have the same pathogenesis.[108]

(III) Regarding the third, autoimmune theory about the fundus lesions in Fuchs' heterochromic cyclitis; In addition to the toxoplasmosis-like scars, non-specific chorioretinal scars and histoplasmosis-like scars were found in patients with Fuchs' heterochromic cyclitis.[27,110] Moreover, Arffa and Schlaegel[110] described two patients with Fuchs' heterochromic cyclitis who had fundus lesions characteristic of toxoplasmosis, but negative titers for toxoplasmosis in undiluted serum. According to Rothova et al. a negative test result (by ELISA and Sabin-Feldman dye-test) with undiluted serum in adults indicates that ocular toxoplasmosis is highly improbable.[124] Arffa and Schlaegel therefore suggested that the chorioretinal scars were of non-Toxoplasma origin and could result from autoimmunity against retinal or choroidal antigens. In support of this hypothesis, La Hey et al.[125] found that a significantly higher percentage of patients with Fuchs' heterochromic cyclitis (with and without chorioretinal scars) had a positive cellular autoimmune response to human retinal S-antigen than healthy controls or other patients with anterior uveitis. Recently, the presence of messenger RNA (mRNA) of S-antigen was demonstrated in irides obtained from uveitis patients and not in control irides.[126] This finding indicates a possible role for S-antigen in anterior segment inflammation and could account for the fact that some patients with Fuchs' heterochromic cyclitis without chorioretinal scars had a positive cellular immune response to S-antigen. Both Fuchs' heterochromic cyclitis and unilateral retinal pigment epithelial changes identical to retinitis pigmentosa have been reported in bilateral ocular toxoplasmosis.[127] Moreover, unilateral Fuchs' heterochromic cyclitis has been reported in association with a bilateral retinitis pigmentosa-like clinical picture.[128-130] It is not known how these three clinical pictures (Fuchs' heterochromic cyclitis, retinal pigment epithelial changes as seen in retinitis pigmentosa, and ocular toxoplasmosis) are related, but it is important to keep in mind that ocular toxoplasmosis may be complicated by a complete retinal vascular occlusion, creating a clinical condition that is very similar to that seen in retinitis pigmentosa.

Vascular Theory

Based on clinical and histopathological findings, a vascular pathogenesis involving the iris vessels has been proposed as a possible cause for Fuchs' heterochromic cyclitis. The first vascular abnormality described in patients with Fuchs' heterochromic cyclitis, was the characteristic filiform haemorrhage (Amsler's sign) seen after anterior chamber paracentesis.[40] Fragile (newly-formed) vessels in the chamber angle and on the peripheral iris were held responsible for this bleeding.[4,5,40] Amsler and Verrey also found a significant

increase in the permeability of the blood-aqueous barrier,[33] which is made up of the tight-junctions in the iris capillaries and the zonula occludentes at the apex of the non-pigmented epithelial cells of the ciliary body.[131] Iris fluorescein angiographic studies[34-36] showed profound fluorescein leakage from iris vessels, but also delayed filling defects, indicating areas of ischemia, in patients with Fuchs' heterochromic cyclitis. These areas of ischemia were frequently associated with neovascularization. Earlier, light microscopic studies had shown abnormal hyalinization and sometimes endothelial proliferation of the iris vessel walls, with narrowing of the vessel lumen.[1,4,20,29,70,72] Not only the vessels of the chamber angle and iris seem more fragile in Fuchs' heterochromic cyclitis, but also the conjunctiva, upon incision, was observed to bleed more easily than usual.[74]

First, it was proposed that the abnormalities of the iris vessels were caused by a dysfunction of the sympathetic nervous system. This was based on the fact that innervation of the iris vessels is derived solely from the sympathetic (adrenergic) nervous system.[66,132] Some authors suggested a hereditary origin, others thought of a congenital anatomical failure that could be responsible for such a sympathetic dysfunction.[36,79,103,105,133] As a result of this sympathetic dysfunction, permeability of the iris vessels would be increased, but also changes in the vascular supply to the melanocytes of the iris would influence their metabolism, and ultimately, their survival.

The following objections have been mentioned earlier: (1) HLA- and family studies have failed to show a hereditary basis for Fuchs' heterochromic cyclitis. [103-106]
(2) Until now, no evidence has been provided for a selective, unilateral, anatomic defect of the sympathetic nervous system (trophic fibers), which is inherited or contracted during pregnancy.

A second hypothesis suggested that an immune complex vasculitis caused the vascular abnormalities in the iris. It was proposed that the narrowing and hyalinosis of the iris vessel lumen, was the result of a deposition of immune complexes.[4,134] This assumption was based on the detection of circulating immune complexes in the aqueous humor and serum of patients with Fuchs' heterochromic cyclitis.[135,136] These immune complexes could result from a deposition of circulating immune complexes in the iris vessel walls.[4] It was suggested that a reduced suppressor T-cell function, demonstrated in the serum of patients with Fuchs' heterochromic cyclitis,[136,137] would lead to overstimulation of B-cells and production of low-affinity antibodies with subsequent immune complex formation.[4,134]

Points that must be considered are the following: (1) In general, the role of immune complexes in the pathogenesis of uveitis is controversial. In the earlier literature, many authors speculated that immune complex deposition could lead to an intraocular inflammatory response and that the recurrence of uveitis resulted from the repeated deposition of immune complexes in the uveal tract.[138-141] More recent studies indicate that immune complexes may represent a compensating mechanism in autoimmune diseases.[142,143] (2) An unusual technique to detect immune complexes was used by Dernouchamps et al.[135] to demonstrate the immune complexes in the aqueous humor of patients with Fuchs' heterochromic cyclitis. It is

therefore necessary to confirm their findings with standard immune complex assays. (3) Fuchs' heterochromic cyclitis is usually an unilateral disease and when circulating immune complexes are implicated in its pathogenesis, there must be factors in the vessel wall (vascular endothelium) of the already affected iris that promote binding of immune complexes.[4] (4) Patients with Fuchs' heterochromic cyclitis are generally free of the more commonly encountered systemic manifestations of immune complex vasculitis, such as arthritis, glomerulonephritis, or scleritis.

Thus, it is more likely, if immune complexes are involved in the pathogenesis of Fuchs' heterochromic cyclitis, that intraocular factors may be responsible for the local formation of immune complexes in the vessel wall.[4] Plasma cells found in the iris,[1,4,18,55,66,68-74] may be responsible for the local production of antibodies. As suggested by O'Connor,[4] these plasma cells may somehow escape the normally imposed regulation by T-lymphocytes. An intraocular "B-cell factory" may result, which produces a large amount of immunoglobulins and low-affinity antibodies with subsequent intraocular immune complex formation. In Fuchs' heterochromic cyclitis, in addition to the above mentioned plasma cells and immune complexes, a local production of immunoglobulins (IgG and IgE) has been demonstrated in the aqueous humor.[21,144-147] Mast cells have been found in the iris of patients with Fuchs' heterochromic cyclitis.[66,73] They may be involved in initiating immune complex deposition by producing substances that increase vascular permeability.[134] It is well known that immunoglobulin E may trigger mast cells to produce such vaso-active substances.[148]

Recently, deposits of immunoglobulins and complement, indicating the presence of immune complexes, were found in the vessel walls of the iris from patients with Fuchs' heterochromic cyclitis.[149] However, no light-microscopic evidence for an inflammatory vascular process could be detected:[149] there was no neutrophilic or lymphocytic and plasmacellular invasion of the vessel wall with fibrinoid necrosis or fibrous thickening.[150,151] These immune deposits were also found in other types of uveitis, but not in the irides of patients with glaucoma without uveitis. Further studies are therefore necessary to determine the pathogenic role of these immune deposits and to find out whether they result from local formation or originate from the circulation.

Immunologic Theory

The presence of plasma cells and lymphocytes in the iris and aqueous humor of patients with Fuchs' heterochromic cyclitis appears to be a constant finding and supports the hypothesis that Fuchs' heterochromic cyclitis may be a true inflammation of immunologic origin.

The hypothesis that a degradation of uveal tissue following an infection would cause an autoimmune reaction against this (altered) tissue, was one of the earliest immunologic theories. It was based on the finding of anti-uvea autoantibodies at high concentrations in the aqueous humor of patients with Fuchs' heterochromic cyclitis.[152] In a more recent study however, no autoantibodies against human iris tissue could be demonstrated in any of the serum samples obtained from 27 patients with Fuchs' heterochromic cyclitis.[153]

In a recent immunohistochemical study Murray et al.[73] demonstrated in four out of eight irides from patients with Fuchs' heterochromic cyclitis, Interleukin-2 receptor negative T-helper and T-suppressor lymphocytes, B-lymphocytes, and plasma cells. Similar findings were also observed in patients with other types of uveitis. Class II HLA-DR was expressed on iris stromal cells in every patient in the Fuchs' heterochromic cyclitis group and in the uveitis group. No specific immunohistochemical abnormalities could thus be demonstrated in patients with Fuchs' heterochromic cyclitis compared to other types of uveitis.[73] Moreover, in contrast with earlier findings, T-or B-lymphocytes were observed, but not in all iris biopsy specimens. This may be explained by the relatively small size of the iris specimen (peripheral iridectomy) or to the fact that only a limited number of T-and B-cell markers were used in this study.

In 1960, the first immunologic abnormalities of the aqueous humor were reported by Francois and Rabaey,[154] who found in seven of their 13 patients with Fuchs' heterochromic cyclitis a relatively increased level of the gammaglobulin fraction by electrophoresis. In 1982, Dernouchamps[144] determined the concentration of various immunoglobulins in the aqueous humor by means of the Relative Concentration Ratio (RCR):

$$\frac{\text{Aqueous IgG / Serum IgG}}{\text{Aqueous albumin / Serum albumin}}$$

A local production of immunoglobulins is present in the aqueous when the RCR for IgG is equal to or higher than 0.65, for IgA $\geq$ 0.60 and for IgM $\geq$ 0.40. Among the various ocular diseases tested (uveitis, intraocular tumors, perforating injuries), Fuchs' heterochromic cyclitis (28 out of 35 patients) was most frequently associated with a relative excess of IgG in the eye.[144]

Later, these findings of intraocular IgG-production in Fuchs' heterochromic cyclitis were confirmed by Murray et al.[146,147] He found intraocular IgG synthesis (RCR > 0.65) in 65 % of his patients, and oligoclonal IgG bands, mainly of the IgG1 subclass, were present in 57 % of his patients with Fuchs' heterochromic cyclitis. Three of his patients with Fuchs' heterochromic cyclitis who had oligoclonal IgG bands however, had a RCR < 0.65, i.e. a low RCR does not exclude intraocular synthesis of IgG, and the IgG:albumin RCR appears not to be such a reliable method for measuring IgG production.[147] Although an intraocular synthesis of IgG was also found in 70 % of the other types of uveitis tested (toxoplasma uveitis and pan-or posterior uveitis of unknown origin), no oligoclonal IgG response was found in the aqueous humor of these uveitis patients. These oligoclonal IgG bands in Fuchs' heterochromic cyclitis, may imply that a small number of intraocular B-cells is stimulated by an, as yet unidentified specific antigen.[146,147] Whether this antigen is part of an infectious agent, or an intraocular auto-antigen, remains to be determined.

Furthermore, Murray et al. demonstrated local production of the cytokine interleukin-6 (IL-6), which is a potent inflammatory mediator, in the aqueous humor of 63 % of the

patients with Fuchs' heterochromic cyclitis, but also in 70 % of the other types of uveitis (toxoplasma uveitis and pan-or posterior uveitis of unknown origin).[146,155] The locally produced IL-6 in Fuchs' heterochromic cyclitis may stimulate specific B-cell clones, thereby leading to the oligoclonal IgG production seen in some patients.[155]

An increased level of soluble interleukin-2 receptor (IL-2R), a marker of (T-) lymphocytic activation, was recently measured in the peripheral blood of patients with Fuchs' heterochromic cyclitis.[156] Although this increased level of IL-2R is not specific, it indicates a systemic lymphocytic activation in this (usually unilateral) eye disease.

Another conspicuous immunologic abnormality in Fuchs' heterochromic cyclitis was reported by van der Gaag et al.:[157] 70 % of all patients with Fuchs' heterochromic cyclitis showed a cellular autoimmune response against a major corneal antigen (54 kD; aldehyde dehydrogenase). Only 40 % of patients with other types of anterior uveitis, 14 % of the patients with posterior uveitis, 25 % of the patients with panuveitis of various etiologies, and 5 % of the normal controls had a cellular immune response against this 54 Kd antigen.[157] Humoral immunity to this 54 Kd corneal antigen was found in 50 % of the patients with Fuchs' heterochromic cyclitis.[157] Autoantibodies against corneal epithelium were recently demonstrated in almost 90 % of the patients with Fuchs' heterochromic cyclitis.[153] It was hypothesized that the typical keratic precipitates in patients with Fuchs' heterochromic cyclitis may consist of lymphocytes specially sensitized to such antigens on the corneal endothelium. Perhaps these sensitized cells leave the iris blood vessels, when their permeability is increased during inflammation, and find their target antigen in the anterior chamber.[145]

In addition to this peripheral sensitization against a corneal antigen, cellular autoimmunity against human retinal S-antigen was found in almost 50 % of the patients with Fuchs' heterochromic cyclitis.[125] In an earlier study, three out of four patients with Fuchs' heterochromic cyclitis and cataract showed a hypersensitivity to α-crystalline, a lens-antigen.[158] Patients with senile cataract or herpetic uveitis showed no reactions.[158]

No abnormalities have been detected in any of the following immunologic parameters in the peripheral blood of patients with Fuchs' heterochromic cyclitis: Immunoglobulin G, IgA, IgM, Rheumatoid Factor, C-reactive protein, anti-nuclear antibodies, anti-smooth muscle antibodies, anti-gastric parietal cell antibodies, anti-lens antibodies, total lymphocyte count, total number of T-cells, number of helper or suppressor T-cells, or soluble serum ICAM-1, a circulating adhesion molecule.[136,159-161]

It is difficult to combine all the above mentioned immunologic abnormalities into one pathogenic mechanism. The oligoclonal IgG bands in the aqueous humor of patients with Fuchs' heterochromic cyclitis seem to be a specific finding, indicating that a small number of intraocular B-cells is stimulated by a specific (still unknown) antigen. The high incidence of systemic sensitization against various ocular antigens in these patients is remarkable.

Therapy and Prognosis

Corticosteroid therapy

Although the use of corticosteroid drops may diminish the clinical signs of inflammation in Fuchs' heterochromic cyclitis, this chronic disease is never cured by such treatment.[6] Visual acuity may improve slightly by local corticosteroid therapy, by reducing the number of keratic precipitates on the central part of the cornea, or by a decrease in the inflammatory activity in the anterior chamber. The major change in visual acuity however, is often due to cataract, and long-term topical corticosteroid therapy may only hasten cataract formation.[59] No controlled study has been performed on the use of topical steroids in Fuchs' heterochromic cyclitis. Since no substantial benefit for such treatment has been reported,[162] it is best to reserve treatment for the cases mentioned above, in whom some improvement of visual acuity may be expected.

Cataract Extraction

In the earlier literature, the results of cataract extraction varied considerably. Fuchs, and later Franceschetti found excellent results and the restoration of good vision after cataract surgery.[1,20] Ward and Hart[163] in 1967 were the first to report serious complications after cataract extractions (9 patients; six intracapsular procedures and three extracapsular procedures). They suggested that lens extractions in these patients resulted in an increased intraocular pressure due to a further obstruction of an already embarrassed outflow system by blood, lens breakdown products, and the surgical destruction of part of the filtration system. This view was supported by Norn,[164] and by Liesegang,[23] who reported that the concurrent damage from glaucoma was the major long-term complication after cataract extraction. In 1974 Smith and O'Connor[165] published a more extensive study on 29 patients operated for cataract (23 intracapsular procedures and 6 extracapsular procedures) with much better results. Later studies of Mills and Rosen[166] in 1982 (8 patients; all intracapsular cataract extractions with iris supported intraocular lenses), Gee and Tabbara[167] in 1989 (16 patients; all extracapsular cataract extractions, in 11 cases with posterior chamber intraocular lenses), and Baarsma et al.[168] in 1991 (22 patients; all extracapsular cataract extraction with posterior chamber intraocular lens; Pearce tripoid lens) reported favourably on cataract extraction with intraocular lens implantation.

In these latter studies, the reported incidence of permanent intraocular pressure elevation, developing at some time following operation, varied between 3 and 35 % in patients with Fuchs' heterochromic cyclitis.[4,23,165-174] In other uveitis entities glaucoma develops in a similar percentage after cataract surgery.[162] Since glaucoma has been reported in 12 to 25 % of the unoperated eyes with Fuchs' heterochromic cyclitis,[42-50] the reported incidence rate following surgery may actually reflect the natural course of the disease.[167,169]

In addition to glaucoma, hyphema was a frequent (up to 75 %) intraoperative or postoperative complication reported after cataract extractions in patients with Fuchs' heterochromic cyclitis.[23,163,164] The origin of this hyphema is obscure. Although abnormal vessels were seen in the iris and chamber angle in these patients with Fuchs' heterochromic cyclitis, their presence appeared to be a relatively poor indicator of the development of hyphema following surgery.[169] Recent articles mention a lower incidence of hyphema, which may reflect the use of (improved) microsurgical techniques and a switch to extracapsular cataract surgery.[166-172]

A third frequently reported complication (also in later studies) after cataract surgery in patients with Fuchs' heterochromic cyclitis was progressive vitreous opacification. This vitreous reaction appears to respond poorly to corticosteroid therapy.[23,169]

In a recent study, Jones suggested that the implantation of a posterior chamber lens following extracapsular cataract extraction in "high-risk" cases, such as patients with severe iris atrophy or preexisting glaucoma, should be avoided, and that postoperative anti-glaucoma medication should be used routinely in such cases.[173]

Most authors, however, now agree that cataract extraction with or without the implantation of an intraocular lens (posterior chamber lens or iris supported lens), has no adverse effect on the development of postoperative complications in patients with Fuchs' heterochromic cyclitis, and that in eyes with preexisting glaucoma, the control of intraocular pressure is not altered postoperatively.[51,168-170,172] These favourable results may be due to the progress in microsurgical techniques and the switch to extracapsular surgery. The use of phacoemulsification and in the bag implantation may further improve the results and diminish postoperative complications. In addition to the postoperative use of topical steroids, or betamethason injected in a parabulbar manner, the use of corticosteroid drops for a few weeks prior to surgery, to achieve minimal or no anterior chamber reaction at the time of the cataract extraction, is recommended.[169,174]

Glaucoma

Many studies primarily report on the prevalence of secondary glaucoma in Fuchs' heterochromic cyclitis. Glaucoma occurred more frequently in blacks,[27] in cases with bilateral involvement,[44] and in female patients.[48] Few authors described their experience in the management of glaucoma.[23,48-51] Lemke suggested that the prognosis for glaucoma was better in patients with Fuchs' heterochromic cyclitis, when the intraocular pressure elevation was treated early.[47] Most studies agree that glaucoma usually becomes refractory to medical treatment.[23,49-51] Jones however, recently concluded from his series that medical therapy is not any less likely to succeed in Fuchs' heterochromic cyclitis than in other forms of glaucoma.[48]

In general, it is known that filtering surgery has a lower chance of success in patients with uveitis, not only because of the younger age of these patients (and thus a more vigorous

wound healing), but also because inflammatory mediators may promote fibrous tissue growth and closure of the filtering bleb.[6]

Three authors reported on glaucoma surgery in Fuchs' heterochromic cyclitis: two of these three claimed only moderate success.[23,48,49] They all used various surgical techniques and reported their results after a short (or not mentioned) follow-up, without information on visual field, visual acuity or optic disk. In the series of Liesegang,[23] successful control of intraocular pressure was obtained in 12 (57 %) of the 21 patients with Fuchs' heterochromic cyclitis and glaucoma, after one filtering operation. Jones[48] reported satisfactory control of intraocular pressure (no criteria were mentioned) in three out of six cases after a single procedure, and in three others after a total of nine glaucoma operations. A third study reported that all six surgical procedures carried out in five patients with Fuchs' heterochromic cyclitis, only resulted in a short term hypotensive effect, followed by intractable ocular hypertension.[50]

After a mean follow-up of 26 months, La Hey et al.[51], recently reported successful control of intraocular pressure in 13 (72 %) out of 18 patients, by performing mostly trabeculectomies with modern surgical techniques (use of fibrosis inhibitors and sodium hyaluronate). All successfully operated patients retained a visual acuity of 20/80 or better, although approximately 50 % showed progression of visual field and/or optic disc damage.[51] The use of anti-metabolites such as 5-fluorouracil or mitomycin C, with a toxic effect on the growth of fibrous tissue, seems to have a beneficial effect on the surgical outcome of glaucoma surgery in these patients. Long term results, especially with respect to visual field loss however, still need to be evaluated.

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Chapter 3

CLINICAL ANALYSIS OF FUCHS' HETEROCHROMIC CYCLITIS

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Summary- Fuchs' heterochromic cyclitis is an important diagnosis to make. Not only for the patient, because incorrect diagnosis may lead to unnecessary therapy and the failure to detect secondary glaucoma, but also for the comparison of studies on the etiology of Fuchs' heterochromic cyclitis, which is still unknown. No clinical criteria for establishing the diagnosis of Fuchs' heterochromic cyclitis have been internationally accepted yet. By means of clinical analyses of Fuchs' heterochromic cyclitis patients in different parts of the world, predominant clinical features may be distinguished and combined to form (internationally accepted) diagnostic criteria. We report a clinical analysis of 51 Fuchs' heterochromic cyclitis patients in the Netherlands: acute symptoms (severe redness, pain or photophobia) were never (100%) encountered. Characteristic keratic precipitates (88%) and/or minimal aqueous cells and flare (60%) and/or vitreous opacities (84%) were major signs, indicating a chronic inflammatory activity, in which no synechiae (100%) were present. Heterochromia (82%) was not a constant sign, but iris stromal atrophy, which causes the heterochromia, was always present (100%). Cataract was present in 82% as a result of the chronic iridocyclitis. Secondary glaucoma was present in 22%. Based on the predominant clinical findings obtained from this analysis of Fuchs' heterochromic cyclitis patients, and on data in the literature, we propose clinical diagnostic criteria for Fuchs' heterochromic cyclitis. Future studies, also including other uveitis groups, are necessary to confirm these diagnostic criteria.

Introduction

Many reports have been published on heterochromic cyclitis, since Ernst Fuchs first described this disease in 1906[1]. The main purpose of these studies was to elucidate the etiology of Fuchs' heterochromic cyclitis, which is still unknown. Many authors used the classical triad of signs, first described by Kimura, Hogan and Thygeson in 1955[2], as a basis on which Fuchs' heterochromic cyclitis patients were selected. This classical triad consists

of heterochromia, a mild chronic cyclitis and cataract. Heterochromia may be absent. The atrophic alterations in the iris stroma, however, which cause the heterochromia, are a constant sign. In advanced cases transpupillary retro-illumination may reveal a defective posterior pigment epithelium of the iris ("moth-eaten" appearance). The presence of floaters in the vitreous, minimal flare and cells in the aqueous, and small white keratic precipitates scattered on the entire endothelium, indicate a mild inflammatory activity. Cataract develops as the result of a longstanding cyclitis[2].

The diagnosis of Fuchs' heterochromic cyclitis is difficult because the various clinical signs are not always present at the same time. No clinical criteria for establishing the diagnosis of Fuchs' heterochromic cyclitis have been internationally accepted yet.

Dernouchamps reported the incidence of clinical features in 550 Fuchs' heterochromic cyclitis patients studied by the International Uveitis Study Group (IUSG)[3].

Tabbut et al.[4] proposed diagnostic criteria for Fuchs' heterochromic cyclitis in a study on Fuchs' heterochromic cyclitis in blacks. They concluded that in blacks, Fuchs' heterochromic cyclitis may be overlooked because of the frequent lack of obvious heterochromia in dark brown irides.

In a clinical study on Fuchs' heterochromic cyclitis from Brazil[5], presented at the World Uveitis Symposium in Sao Paulo in 1988, a very low percentage of Fuchs' heterochromic cyclitis patients was reported to have iris stromal atrophy. Moreover, the presence of vitreous opacities, which is an important clinical sign, was not mentioned.

Fuchs' heterochromic cyclitis is an important diagnosis to make for the patient, because incorrect diagnosis may lead to unnecessary therapy and the failure to monitor intraocular pressure regularly, so that secondary glaucoma may not be detected[4]. Furthermore, if authors use different diagnostic criteria, the results of studies on the etiology cannot be compared. It is therefore necessary to determine internationally accepted diagnostic criteria. By means of clinical analyses of Fuchs' heterochromic cyclitis patients in different parts of the world, the predominant clinical findings may be distinguished and combined to form internationally accepted clinical diagnostic criteria. This is very important, since no diagnostic laboratory test(s) are yet available to confirm the diagnosis of Fuchs' heterochromic cyclitis.

The aim of the present study was to make a clinical analysis of Fuchs' heterochromic cyclitis patients in the Netherlands.

Subjects and methods

After reviewing their histories, a total of 72 patients with a presumable (previously made) diagnosis of Fuchs' heterochromic cyclitis were requested to attend an ophthalmological (re-)examination. All 72 patients were seen at the Rotterdam Eye Hospital in 1990 by two ophthalmologists (Baarsma, de Vries), with clinical expertise on uveitis and Fuchs' heterochromic cyclitis in particular.

The presence of circumcorneal or conjunctival congestion, of keratic precipitates (and their characteristics), of cells and flare in the aqueous, and of floaters in the anterior vitreous

was classified for all 72 patients according to the grading system of Hogan, Kimura and Thygeson[6] (Table 1).

Table 1- Classification of keratic precipitates (KP), cells and flare in the aqueous, and vitreous opacities, according to Hogan, Kimura, and Thygeson.[6]

Grade	KP, cells*	Flare*	Vitreous opacities
0	None	None	None
1	0 - 10	Faint: barely detectable	Few scattered fine + coarse opacities: fundus clearly seen
2	10 - 20	Moderate: iris + lens details clear	Scattered fine + coarse opacities: fundus details somewhat obscured
3	20 - 50	Marked: iris + lens hazy	Many opacities with marked blurring of fundus
4	> 50	Intense: fixed, coagulated aqueous humour with considerable fibrin	Dense opacities which prevent a view of the fundus

*per slit-lamp microscopic field.

Heterochromia, iris stromal atrophy and atrophy of the posterior pigment epithelium of the iris were described. The presence of iris nodules and the presence or absence of synechiae were noted.

Cataract was classified according to the Lens Opacities Classification System (LOCS), as described in detail by Chylack et al..[7]

Furthermore, fundus examination was performed on both eyes of all Fuchs' heterochromic cyclitis patients. In particular, cystoid macular edema, studied by means of a 90D-lens, chorioretinal lesions and a glaucomatous optic disc were noted, and if present described.

In addition, an extensive general and ophthalmological medical history was obtained from all 72 patients.

After examination of the patient, the above ophthalmologists determined if the previous clinical diagnosis of Fuchs' heterochromic cyclitis was "definite", "probable" or "doubtful". Subsequently the clinical findings of the Fuchs' heterochromic cyclitis patients who had been classified as "definite" (n=51) were analyzed. Patients classified as "probable" or "doubtful", that is, if the diagnosis of Fuchs' heterochromic cyclitis was not certain (n=18), and patients whose data were incomplete (n=3), were not included in this analysis.

Results

Of the fifty-one Fuchs' heterochromic cyclitis patients, 30 (59%) were male and 21 (41%) were female. The mean age of all 51 Fuchs' heterochromic cyclitis patients was 40 years, ranging from 17 to 71 years. Two (4%) patients had bilateral Fuchs' heterochromic cyclitis. Forty-eight Fuchs' heterochromic cyclitis patients were white, one patient originally came from Turkey, and two patients came from Surinam. The mean disease duration was 10 years, ranging from 0 to 40. The mean age at the onset of disease was 29 years (range: 4-58 years). The mean age at which the diagnosis of Fuchs' heterochromic cyclitis was (previously) made was 34 years (range: 12-64 years) (Fig 1).

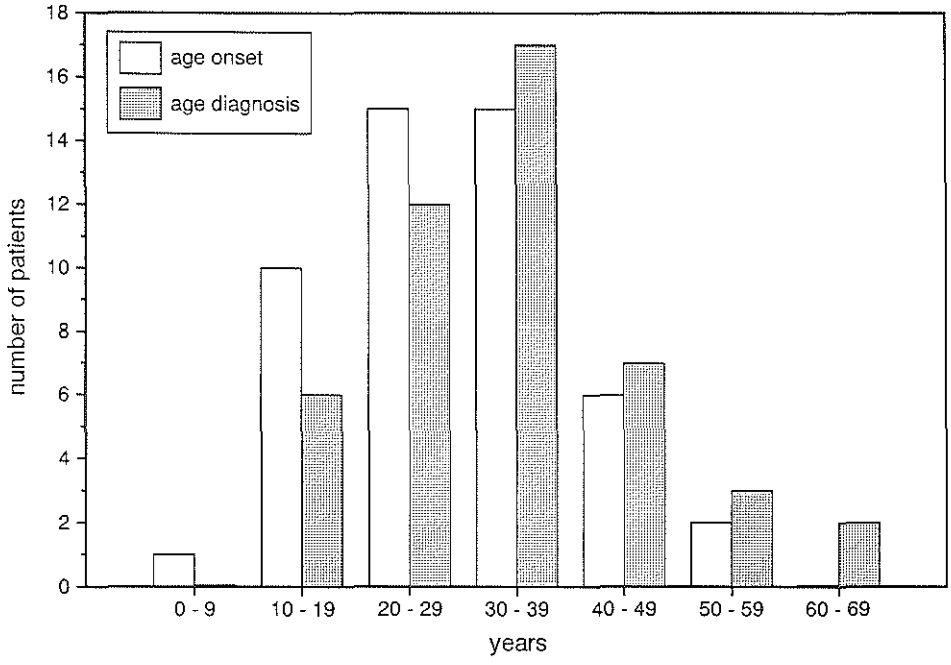

Fig. 1- The age at the onset of disease, and the age at which the diagnosis of Fuchs' heterochromic cyclitis was made.

Best visual acuity, at the moment of our examination, is shown in Fig. 2. Forty-four (86%) of the 51 Fuchs' heterochromic cyclitis patients had a visual acuity better than 0.3. Three patients had a visual acuity of less than fingercounting (< 1/60); one Fuchs' heterochromic cyclitis patient because of dense cataract, two other patients because of corneal disorders (corneal edema and corneal erosion).

Of the 51 Fuchs' heterochromic cyclitis patients, 36 (71%) had no circumcorneal or conjunctival congestion. Fifteen (29%) had slight to moderate circumcorneal congestion (1+).

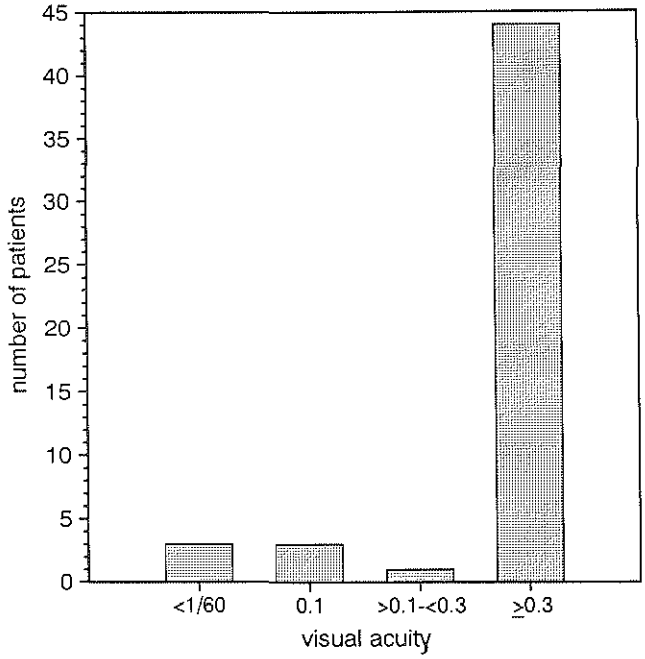

Fig. 2- Best visual acuity of Fuchs' heterochromic cyclitis patients.

Grading of keratic precipitates, and cells and flare in the aqueous humour of all 51 Fuchs' heterochromic cyclitis patients is presented in Fig. 3. In 45 (88%) of all Fuchs' heterochromic cyclitis patients keratic precipitates were present (Table 2). The keratic precipitates were always small white or translucent dots, scattered on the entire endothelium (Fig 4). In approximately 60% of all 51 Fuchs' heterochromic cyclitis patients cells and flare were present in the aqueous (mainly grade 1+).

Heterochromia, with the cyclitic eye lighter-coloured than the non-involved eye, was seen in 42 (82%) of the 51 Fuchs' heterochromic cyclitis patients. Inverse heterochromia, with the Fuchs' cyclitic eye appearing darker than the contralateral, non-involved eye, was seen in one Fuchs' heterochromic cyclitis patient.

In all 51 Fuchs' heterochromic cyclitis patients iris stromal atrophy was present. Iris stromal atrophy in all Fuchs' heterochromic cyclitis patients was diffuse, in contrast with the more focal atrophy seen after a viral disease, such as herpes zoster[6], or herpes simplex.

By transpupillary retroillumination a defective ("moth-eaten") posterior pigment epithelium of the iris, especially in the pupillary zone, was seen in 33 (65%) of the 51 Fuchs' heterochromic cyclitis patients.

Iris nodules were present in five (10%) of the 51 Fuchs' heterochromic cyclitis patients. Four Fuchs' heterochromic cyclitis patients had small white nodules at the pupillary margin (Koeppe nodules; Fig 4B). One Fuchs' heterochromic cyclitis patient had larger white dots, scattered on the anterior surface of the iris, especially in the sphincter area (Busacca nodules; Fig 5).

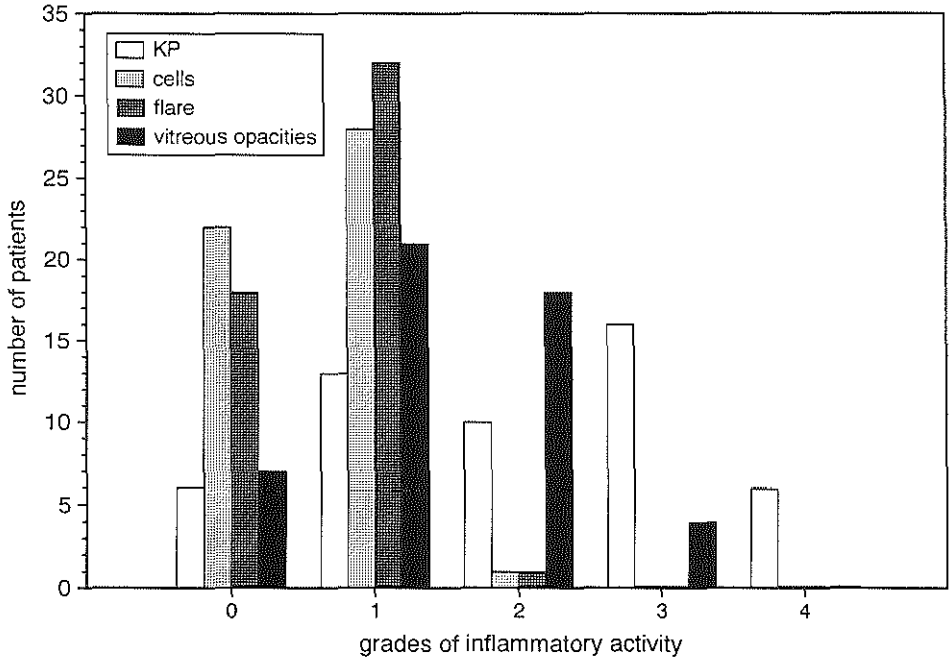

Fig. 3- Classification of inflammatory activity in Fuchs' heterochromic cyclitis patients, according to the grading system presented in Table 1.

Posterior synechiae were absent in all 51 Fuchs' heterochromic cyclitis patients.

Nine (18%) of 51 Fuchs' heterochromic cyclitis patients had a clear lens. In 16 (31%) Fuchs' heterochromic cyclitis patients cataract, and in 26 (51%) Fuchs' heterochromic cyclitis patients surgical aphakia was present. According to the cataract classification system (LOCS), the most frequent cataract was a posterior subcapsular opacity. In a few cases some nuclear opalescence was also present.

Vitreous opacities were present in 43 (84%) of the 51 Fuchs' heterochromic cyclitis patients. Approximately 90% of these vitreous opacities were graded as 1+ or 2+ (Fig 3).

Non-active chorioretinal scars were found in ten (20%) of the 51 Fuchs' heterochromic cyclitis patients. Four of these ten scars were clinically consistent with toxoplasmosis. In six patients nonspecific chorioretinal lesions were seen, not consistent with a specific uveitis syndrome. These lesions were usually very small (half disc diameter) pigmented chorioretinal scars or areas of chorioretinal atrophy of unclear origin, often located in the periphery. Ninety percent of all scars were found in the involved, cyclitic eye.

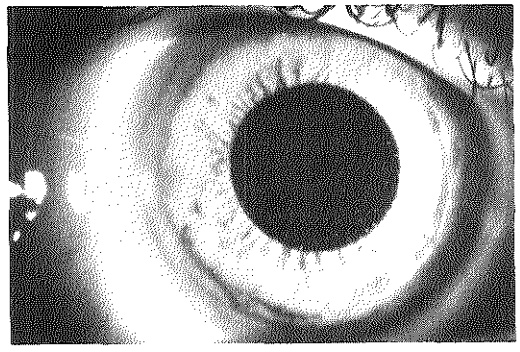

Fig. 4A- Characteristic small white or translucent keratic precipitates, scattered on the entire endothelium.

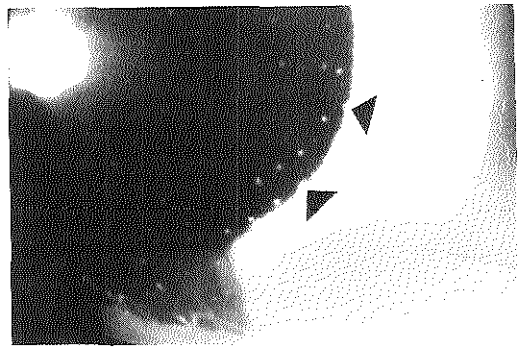

Fig. 4B- Detail of the keratic precipitates. Note the two Koeppe iris nodules at the pupillary margin (4 and 5 o'clock).

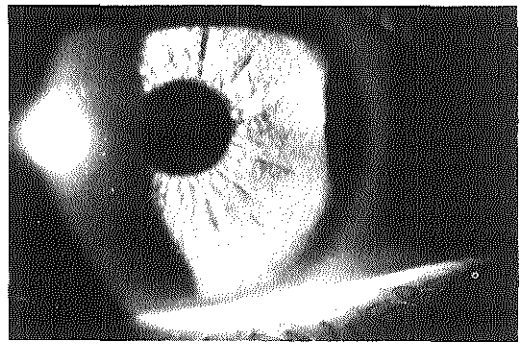

Fig. 5- Busacca iris nodules found in one Fuchs' heterochromic cyclitis patient: large white dots scattered on the anterior surface of the iris, especially in the sphincter area.

Table 2- Clinical features of Fuchs' heterochromic cyclitis patients in different studies.

Clinical features	This study, The Netherlands, n=51	Dernouchamps[3] IUSG, n=550	Tabbut et al.[4] United States, black FHC, n=13	Silva et al.[5], Brazil, n=132
Age: mean (range) yrs.	40 (17 - 71)	34 (8 - 73)	-	38 (11 - 75)
Sex (M:F)	1 : 0.73	-	-	1 : 1.4
Bilaterality	4 %	8 %	0 %	21 %
Keratic precipitates	88 %	96 %	100 %	99 %
Cells / flare aqueous	60 %	-	-	60 %
Heterochromia	82 %	87 %	76 %	34 %
Iris stromal atrophy	100 %	-	61 %	18 %
IPE atrophy	65 %	-	-	-
Iris nodules	10 %	-	30 %	-
Absence synechiae	100 %	-	-	94 %
Cataract / surgical aphakia or pseudophakia	82 %	84 %	23 %	70 %
Vitreous opacities	84 %	69 %	-	-
Glaucoma	22 %	19 %	38 %	19 %
Chorioretinal lesions	20 %*	-	23 %†	28 %‡
Cystoid macular edema	2 %	-	-	-

FHC = Fuchs' heterochromic cyclitis, IPE = iris posterior pigment epithelium
* Non-active scars, 8% "toxoplasma-like" scars. † Non-active scars, no "toxoplasma-like" scars.
‡ 6 active chorioretinal lesions, 31 scars (the type of lesion is not mentioned)

Cystoid macular edema was present in one of the 51 Fuchs' heterochromic cyclitis patients at the time of our examination. In one patient a history of cystoid macular edema was documented and in one other Fuchs' heterochromic cyclitis patient the cystoid macular edema was a possible complication of an extracapsular cataract extraction (Irvine-Gass syndrome).

Glaucoma was found in 11 (22%) of the 51 Fuchs' heterochromic cyclitis patients. Patients were considered to be glaucoma suspects or to have uveitic glaucoma either on a history of anti-glaucoma therapy, or if intraocular pressure was above 21 mm Hg at more

than one examination, as described elsewhere[8]. Glaucomatous visual field defects were present in six of the 11 (uveitic) glaucoma patients.

General and ophthalmological medical histories of all 51 Fuchs' heterochromic cyclitis patients revealed no remarkable events. Heterochromia was present since birth or childhood in seven (14%) Fuchs' heterochromic cyclitis patients. The family histories of the 51 patients revealed no additional cases of Fuchs' heterochromic cyclitis. Two relatives of two Fuchs' heterochromic cyclitis patients however, had congenital heterochromia. No acute symptoms, like severe redness, pain or photophobia, were found in Fuchs' heterochromic cyclitis patients. Visual deterioration, either due to cataract (28 : 55%), or to vitreous opacities (8 : 16%), or a combination of the two (12 : 23%), caused Fuchs' heterochromic cyclitis patients to visit an ophthalmologist for the first time. The three other Fuchs' heterochromic cyclitis patients were first seen at a routine medical examination.

Discussion

Fuchs' heterochromic cyclitis is an important diagnosis to make for the patient, for the following reasons: (1) Patients with Fuchs' heterochromic cyclitis are at risk of developing secondary glaucoma. They need to be monitored regularly, so that glaucoma may be detected early.[4] (2) Uveitis patients are often treated with corticosteroids. Because corticosteroids reduce the inflammatory activity in Fuchs' heterochromic cyclitis patients only minimally[4,9], and they may enhance the tendency of these patients to develop cataract and glaucoma, corticosteroids should be prescribed to Fuchs' heterochromic cyclitis patients with caution. (3) Fuchs' heterochromic cyclitis has a fairly good prognosis. Cataract extractions are generally tolerated well by Fuchs' heterochromic cyclitis patients and result in the restoration of good vision.[10,11] Unilateral cases of Fuchs' heterochromic cyclitis have not been reported to become bilateral. Only glaucoma, which is a complication occurring in approximately 20%[3], is difficult to control therapeutically.[9]

Internationally accepted diagnostic criteria are necessary for the comparison of studies on the etiology of Fuchs' heterochromic cyclitis. Because Toxoplasma gondii has been suggested as a possible agent in the pathogenesis of Fuchs' heterochromic cyclitis, it is important to compare studies on the incidence of "toxoplasma-like" lesions in Fuchs' heterochromic cyclitis patients. The first to report this association of Fuchs' heterochromic cyclitis with toxoplasmosis were de Abreu et al.[12] in Brazil; 60% of the Fuchs' heterochromic cyclitis patients were reported to have chorioretinal lesions characteristic for toxoplasmosis. In the United States, however, 7.5% of the Fuchs' heterochromic cyclitis patients had chorioretinal scars, clinically consistent with toxoplasmosis.[13] This discrepancy can be explained by the different prevalence of toxoplasma retinochoroiditis in different populations, but also by the fact that the authors have used different diagnostic criteria to select their Fuchs' heterochromic cyclitis patients.

To establish internationally accepted diagnostic criteria, it is important that the clinical findings of Fuchs' heterochromic cyclitis patients, from different parts of the world, are

analyzed, and that predominant clinical findings are distinguished. Table 2 summarizes the results of clinical analyses of Fuchs' heterochromic cyclitis patients in various studies. All these studies reported a lower percentage of chorioretinal lesions in Fuchs' heterochromic cyclitis patients than the originally reported incidence of 60% by de Abreu et al..[12] Silva et al[5] reported a lower percentage of heterochromia and iris stromal atrophy in their Fuchs' heterochromic cyclitis patients, and a higher percentage of bilateral cases, in comparison with the other studies presented in Table 2. In the current study the percentage of keratic precipitates was somewhat low when compared with the other three studies. This may be due to the fact that a large number of our Fuchs' heterochromic cyclitis patients had undergone a cataract extraction. After a cataract extraction the precipitates may disappear temporarily.

The percentage of iris nodules (Koeppe and Busacca) reported by Tabbut et al.[4] was higher than in our study. Tabbut et al. concluded in their study on Fuchs' heterochromic cyclitis in blacks, that the frequent presence of iris nodules coupled with the frequent lack of obvious heterochromia in black Fuchs' heterochromic cyclitis patients may lead to an incorrect diagnosis of chronic granulomatous iridocyclitis.

The presence of vitreous opacities, an important clinical sign, was not mentioned in two studies[4,5]. The incidence of macular edema, only reported in our own series, seems to be lower in Fuchs' heterochromic cyclitis than in other forms of chronic iridocyclitis. Tabbut et al.[4] demonstrated a significantly higher incidence of glaucoma and a significantly lower incidence of cataract in black Fuchs' heterochromic cyclitis patients than in white Fuchs' heterochromic cyclitis patients. More studies with larger numbers of black patients are necessary to confirm this finding.

Based on the predominant clinical findings obtained from the analysis of our 51 "definite" Fuchs' heterochromic cyclitis patients (Table 2) and on data in the literature,[1,4,9,10,14] we composed clinical diagnostic criteria for Fuchs' heterochromic cyclitis, which are presented in Table 3. Essential findings must all be present, and of the associated findings at least two must be present, for the diagnosis of Fuchs' heterochromic cyclitis to be made.

To decide whether these diagnostic criteria are specific for Fuchs' heterochromic cyclitis it is important to apply them to other forms of uveitis. The Posner-Schlossman syndrome, pars planitis, sarcoidosis and panuveitis are sometimes difficult to differentiate from Fuchs' heterochromic cyclitis. Future studies, also including these uveitis groups, are therefore necessary to confirm the diagnostic criteria proposed in Table 3.

Table 3- Diagnostic criteria for Fuchs' heterochromic cyclitis.

I. Essential features*	II. Associated features†
- Absence of acute signs (severe redness, pain and photophobia)	- Unilaterality of the uveitis - Heterochromia
- Characteristic keratic precipitates and/or minimal cells and flare in the aqueous (1+ or 2+)	- IPE atrophy - Subcapsular cataract - Elevated intraocular pressure
- Diffuse iris stromal atrophy	- Vitreous opacities
- Absence of synechiae	- Chorioretinal lesions

IPE = Iris posterior pigment epithelium * All must be present † At least two must be present.

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Chapter 4

TREATMENT AND PROGNOSIS OF SECONDARY GLAUCOMA IN FUCHS' HETEROCHROMIC CYCLITIS

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Summary- After reviewing the records of 111 patients with Fuchs' heterochromic cyclitis, we studied the therapy and prognosis of secondary glaucoma in 30 (27 %) of these 111 patients who had glaucoma or could be considered as "glaucoma suspects". Maximal medical therapy was unsuccessful in 22 (73 %) of the 30 patients. Surgical intervention (mostly trabeculectomies, half with 5-fluorouracil) successfully controlled intraocular pressure ($\leq$ 21 mm Hg with or without medication) in 13 (72 %) of the 18 operated patients after a mean follow-up of 26 months. All successfully operated patients retained a visual acuity of 20/80 or better. We had favourable results, possibly because of modern surgical techniques (use of 5-fluorouracil, sodium hyaluronate) and/or earlier surgical intervention.

Introduction

Fuchs' heterochromic cyclitis is a low grade chronic non granulomatous uveitis of still unknown etiology with cataract and glaucoma as two major complications. Glaucoma is considered the most serious complication that threatens the visual acuity of the patient,[1] since cataract extractions, with or without intraocular lens implantation, have excellent results in patients with Fuchs' heterochromic cyclitis.[1-9]

The prevalence of secondary glaucoma in Fuchs' heterochromic cyclitis varies markedly and lies between 0 and 59 %.[10-16] The pathogenesis of glaucoma in Fuchs' heterochromic cyclitis is still poorly understood. In most cases it is a chronic open-angle glaucoma.[1] However, peripheral anterior synechiae,[17] neovascularization of the chamber angle,[18,19] phacolytic glaucoma,[20,21] trabeculitis,[1,19,22] and corticosteroid-induced glaucoma[23] have been described as possible causes of secondary glaucoma in Fuchs' heterochromic cyclitis. Light- and electron microscopic studies on the trabecular meshwork in these patients are scarce and controversial. Huber[24] reported an increased outflow resistance with sclerosis

of the trabecular meshwork in Fuchs' heterochromic cyclitis, while Benedikt et al.[25] noted a collapse of the canal of Schlemm with atrophy of its wall.

Only few authors described their experience in the management of glaucoma in Fuchs' heterochromic cyclitis and concluded that it usually becomes refractory to medical treatment.[15,26,27] Three authors reported on glaucoma surgery: two claimed only moderate success.[15,28] A third study reported failure of drainage surgery for glaucoma in all cases.[27] Mostly, small series of operated patients with Fuchs' heterochromic cyclitis were described, with a short follow-up and without information on visual field or visual acuity.[27,28] We studied the results of glaucoma surgery in which modern surgical techniques with fibrosis inhibiting drugs such as 5-fluorouracil or mitomycin c were used.

The aim of this study was to evaluate the therapy and prognosis of secondary glaucoma in Fuchs' heterochromic cyclitis, on the basis of a larger series of patients who had antiglaucoma medication and filtration procedures in which modern surgical techniques were used.

We found that medical therapy was unsuccessful in a high proportion (22 of 30 patients). Glaucoma surgery, mainly trabeculectomies (half with 5-fluorouracil), was successfully carried out in 13 (72 %) of the 18 patients. On the basis of this series, we recommend early surgical intervention and the use of antimetabolites such as 5-fluorouracil in patients with Fuchs' heterochromic cyclitis and glaucoma.

Patients and Methods

We reviewed the charts of all patients with Fuchs' heterochromic cyclitis who were seen at the Eye Hospital Rotterdam and the Department of Ophthalmology of the University of Amsterdam between 1980 and 1992. Fuchs' heterochromic cyclitis was diagnosed on the basis of the following criteria[7,10-15,29]: (1) absence of acute symptoms, such as severe redness, pain or photophobia; (2) presence of characteristic small white stellate keratic precipitates; (3) minimal cells and flare in the anterior chamber; (4) diffuse iris stromal atrophy with or without patchy loss of the iris pigment epithelium; (5) absence of synechiae; (6) presence of cells and opacities in the anterior vitreous. Heterochromia, cataract or glaucoma were not essential criteria for the diagnosis of Fuchs' heterochromic cyclitis.

For the purpose of this study, a patient with Fuchs' heterochromic cyclitis was considered a "glaucoma suspect" if intraocular pressure was above 21 mm Hg at more than two examinations or, if the patient was referred to us with a history of intraocular pressure increase concurrent with intraocular inflammation and had already received anti-glaucoma therapy. This definition included patients with glaucomatous cupping of the optic disk, who had no detectable visual field defects. Patients were considered to have glaucoma if there was evidence of glaucomatous visual field and optic disk damage with a documented increase in intraocular pressure (> 21 mm Hg). No patients had a record of normal tension glaucoma.

A large number of variables was analyzed in the whole group of patients to investigate whether differences could be found between glaucomatous and non-glaucomatous patients

with Fuchs' heterochromic cyclitis: sex, age at initial ophthalmic examination, estimated duration of the cyclitis, number of bilateral cases, follow-up, and factors that may increase the risk of developing glaucomatous damage, such as race, hypertension, cardiovascular disease, diabetes, a family history of glaucoma, myopia and migraine.[30,31] In addition, each chart was reviewed to note previous ocular trauma or surgery, including cataract extraction. With regard to the cataract extraction the following was recorded: whether it had been intracapsular or extracapsular, whether an intraocular lens had been implanted or a peripheral iridectomy had been performed, whether there was a history of preexisting glaucoma and whether there were peri- or postoperative complications such as hyphema, posterior capsule rupture with or without vitreous loss, peripheral synechiae, retinal detachment, persistent cystoid macular edema, or endophthalmitis. Furthermore, we noted whether a Nd:Yag laser capsulotomy was necessary to treat posterior capsule opacification.

Charts of the patients with Fuchs' heterochromic cyclitis who were classified as glaucoma or "glaucoma suspects" were reviewed to determine the following: age at initial examination with initial intraocular pressure increase (> 21 mm Hg), age at diagnosis of glaucoma, whether the anti-glaucoma therapy had consisted of medication alone, and whether additional laser treatment or drainage surgery was performed.

Of the ocular examinations of the patients with Fuchs' heterochromic cyclitis and (suspected) glaucoma, the following data were recorded (at various points in time): best-corrected visual acuity, intraocular pressure, cup/disk ratio and results of gonioscopy and visual field analysis. Data on visual acuity, intraocular pressure and cup/disk ratio were collected at the time of initial intraocular pressure increase or, in patients who were referred to us with a history of intraocular pressure increase, at the first examination in one of the two previously mentioned eye clinics. These data were defined as initial values. Data obtained at the most recent follow-up examination were defined as final values. This information was related to the kind of anti-glaucoma therapy the patient had received and the follow-up time.

For the patients that underwent glaucoma surgery, the last recorded data on visual acuity and intraocular pressure before glaucoma surgery were defined as preoperative values, and data obtained at the most recent follow-up examination were defined as post-operative values. In the patients that underwent further glaucoma surgery, the last visual acuity and intraocular pressure measurements before further glaucoma surgery were defined as postoperative values.

The cup/disk ratio was determined by examination with a 90-diopter lens and biomicroscope. A cup/disk ratio of greater than 0.5 was considered abnormal.[32] Since the cup/disk ratio is not such an accurate parameter[33] and no photographic records were made, only initial and final values, as defined previously, were recorded to study the progression of glaucomatous damage. Because various visual field analyzers were used in both eye clinics between 1980 and 1992, we used a modification of the quantitative grading system of visual field loss described by Watson et al.,[34] and evaluated only large major defects inside 30° (Table 1).

Table 1- Grading of visual field loss.[34]

Grade 1:	Early relative or absolute field defects of any type, between 10° and 30° in all quadrants.
Grade 2:	Absolute field defects within 10° in one quadrant.
Grade 3:	Absolute field defects within 5° in one quadrant.
Grade 4:	Absolute field defects within 5° in two or more quadrants.
Grade 5:	Absolute field defects within 2° in any quadrant.

Of the patients with Fuchs' heterochromic cyclitis who underwent filtration surgery, each chart was reviewed to obtain the following information: (1) the surgical procedure; (2) if the eye underwent previous cataract surgery; (3) if the eye was aphakic or pseudophakic, and if the posterior capsule was intact at the time of surgery; (4) if the eye underwent previous intraocular surgery other than cataract extraction; (5) if there were peripheral anterior synechiae over more than 180° preoperatively; (6) whether the eye had a history of failed glaucoma surgery; (7) if in the same session a vitrectomy or cataract extraction was performed; (8) if subconjunctival injections of 5-fluorouracil were administered postoperatively; (9) whether sodium hyaluronate was used, and (10) the complications and cause of failure of the drainage procedure were noted.

Surgical outcome was categorized as success or failure according to the classification system of Heuer et al.[35]:"complete success: intraocular pressure $\leq$ 21 mm Hg without medication; "qualified success": intraocular pressure $\leq$ 21 mm Hg with medication or intraocular pressure $\leq$ 25 mm Hg without medication; "qualified failure": intraocular pressure $>$ 21 mm Hg with medication or intraocular pressure $>$ 25 mm Hg without medication; and complete failure": reoperation (or recommendation thereof) or loss of light perception.

Statistical analysis was performed by using the Fisher's exact test or Chi-squared test and the Student's t-test to evaluate differences in categoric and continuous variables respectively, between glaucomatous and non-glaucomatous patients, pre-and postoperative values, and successful and failed filtration procedures. For calculation of the cumulative success rate of the surgical procedures, the Kaplan-Meier product limit analysis was used. For this analysis only the first filtration procedure of each patient was included.

Trabeculectomies, double flap Scheie operations and drainage implants were performed by three staf surgeons (J.d.V., C.T.L. and G.S.B.) of the glaucoma departments. No standardized protocol for preoperative treatment of intraocular inflammation was used in this series. At the time of the operation, patients had variable anterior chamber and/or vitreous reaction (ranging from none to moderate). Most patients were treated with topical corticosteroids, miotics, timolol, epinephrine and/or carbonic anhydrase inhibitors preoperatively. None of the patients received systemic corticosteroids. Surgery was

performed under local or systemic anaesthesia. All surgery was performed superonasally or superotemporally.

The surgical technique for the trabeculectomies consisted of a limbal-based conjunctival flap, which was created starting 7 to 8 mm behind the corneoscleral limbus. The conjunctival incision extended over 3 to 4 clock hours. A tenectomy was not performed. A 3 x 3 x 3 mm triangular or 4 x 4 mm rectangular scleral flap, one half of the scleral thickness, was made and approximately 1 x 2 mm anterior chamber angle tissue was excised. Three to five 10-0 nylon sutures were used to suture the scleral flap to the surrounding sclera. Tenon's capsule was closed with three 10-0 nylon sutures. The conjunctiva was closed by using a running, locking 8-0 or 9-0 vicryl suture. For the double flap Scheie operation, a conjunctival and a scleral flap were prepared as in a trabeculectomy, and in addition, a cauterized limbal incision into the anterior chamber was made under this scleral flap. One Krupin-Denver valve was implanted, by using a surgical technique described earlier.[36] Twice (one eye) a Gonioseton according to Worst was implanted, as described elsewhere.[37] In short, after a temporal limbal incision, this seton (a stainless steel micro-spiral implant) is introduced by a hollow needle into a goniopuncture at the opposite side of the anterior chamber. Aqueous then drains automatically into the subconjunctival space to form a filtration bleb. The procedure is completed after retraction of the needle; suturing is not necessary.

No routine postoperative treatment regimen was used in this series. At the end of the operation, triamcinolone acetonide was injected subconjunctivally, or betamethason was injected in a parabulbar manner and gentamicin was administered. In eight trabeculectomies, subconjunctival injections of 5-fluorouracil in 0.5 ml saline solution were given. Subsequently, during the first and second postoperative week, injections of 5 mg 5-fluorouracil in 0.5 ml saline solution were given daily. The injections were discontinued when toxicity, such as corneal epithelial defects or conjunctival wound leak were observed, or when the appearance of the subconjunctival bleb was so favourable that further 5-fluorouracil injections were deemed unnecessary. Topical corticosteroids with varying treatment schedules were used in all patients.

Results

A total of 111 patients fulfilled the criteria for Fuchs' heterochromic cyclitis and were included in this survey. Of these 111 patients (118 eyes), 30 (27 %) patients (fourteen men and sixteen women) had glaucoma or could be considered as "glaucoma suspects". Two patients had bilateral Fuchs' heterochromic cyclitis: one patient had a glaucomatous eye and a 'normal' cyclitic eye, and the second patient had one eye suspected of glaucoma and one glaucomatous eye. Thus, a total of 31 eyes was included: glaucoma occurred in 18 eyes, whereas 13 eyes were classified as glaucoma suspects. Six of the 13 glaucoma suspect eyes had a cup/disk ratio greater than 0.5. Twelve of the 30 patients with Fuchs' heterochromic cyclitis and (suspected) glaucoma were referred to us and had already received anti-glaucoma therapy (medical or surgical) elsewhere.

In this study mean follow-up was 5.9 years on all 111 patients with Fuchs' heterochromic cyclitis. Patients with (suspected) glaucoma had initial ophthalmic examinations at a mean age of 36 years (range 21 to 70 years), and with an initial intraocular pressure increase at a mean age of 43 years (range 22 to 74 years). The diagnosis of glaucoma was made at a mean age of 47 years (range 23 to 76 years). No significant differences were found between the 30 patients with (suspected) glaucoma and the 81 other non-glaucomatous patients with Fuchs' heterochromic cyclitis regarding any of the following: sex-ratio, age at initial ophthalmic examination, duration of the cyclitis, bilateral involvement, or the presence of risk factors (race, hypertension, cardiovascular disease, diabetes, family history of glaucoma, myopia or migraine) .

Cataract surgery had been performed in 18 of the 30 patients with Fuchs' heterochromic cyclitis and (suspected) glaucoma and in 40 of the 81 other (non-glaucomatous) patients with Fuchs' heterochromic cyclitis. No significant differences were found between the glaucomatous group (excluding patients with preexisting glaucoma) and the non-glaucomatous group concerning any of the following: (1) the number of operations or the surgical technique used for the cataract extraction; (2) the number of peri- and postoperative complications or the number of patients that underwent Nd:Yag laser capsulotomy; and (3) the number of patients with a history of ocular trauma or intraocular surgery other than for cataract.

Of the 18 eyes from the glaucoma group that were operated for cataract, six had preexisting glaucoma. In these six eyes, cataract surgery did not influence the (post-operative) management of glaucoma: mean intraocular pressure or the mean number of antiglaucoma medications were not (significantly) higher postoperatively than preoperatively. In one eye a combined procedure (Scheie with extracapsular cataract extraction) was performed, which could still be classified as (qualified) success after 10 years. In the twelve other eyes from the glaucoma group that had cataract surgery, the first intraocular pressure increase occurred after a mean postoperative period of 6.5 years, ranging from immediately postoperative to 32 years postoperative. In two eyes intraocular pressure increase started immediately after Nd:YAG laser capsulotomy. In one of these two eyes Nd:Yag laser capsulotomy caused an exacerbation of the iridocyclitis.

Results of gonioscopy were recorded in 16 eyes with Fuchs' heterochromic cyclitis and (suspected) glaucoma. Eleven eyes had an open angle, eight had fine vessels within the chamber angle, and five eyes had anterior synechiae. In three of these five eyes the anterior chamber angle was more than half closed. Two patients had developed the anterior synechiae after cataract extraction. No patients had an abnormal membrane in the angle. Gonioscopy was performed in only a few of the 81 other non-glaucomatous patients with Fuchs' heterochromic cyclitis; all had open angles.

Treatment in the 13 glaucoma suspect eyes consisted of anti-glaucoma medication alone (eight eyes), laser trabeculoplasty (one eye) and glaucoma surgery (four eyes). Of the 18 eyes

with glaucoma, two received medication alone, two eyes underwent laser therapy and 14 patients had filtration surgery.

Medical treatment consisted of miotics, timolol, epinephrine and carbonic anhydrase inhibitors. Although many patients with Fuchs' heterochromic cyclitis had received topical corticosteroid medication at some stage of their disease, no lasting relation could be found with the development of glaucoma. Only one patient with Fuchs' heterochromic cyclitis was a "corticosteroid responder"; intraocular pressure normalized after corticosteroid medication was stopped. In 22 (73 %) of the 30 patients maximal anti-glaucoma medication (two topical agents with or without carbonic anhydrase inhibitor) was unsuccessful in controlling intraocular pressure. Three of these 22 patients underwent additional Argon laser trabeculoplasty, which was applied in several sessions over 360°. Eighteen patients required surgical intervention; results will be discussed below.

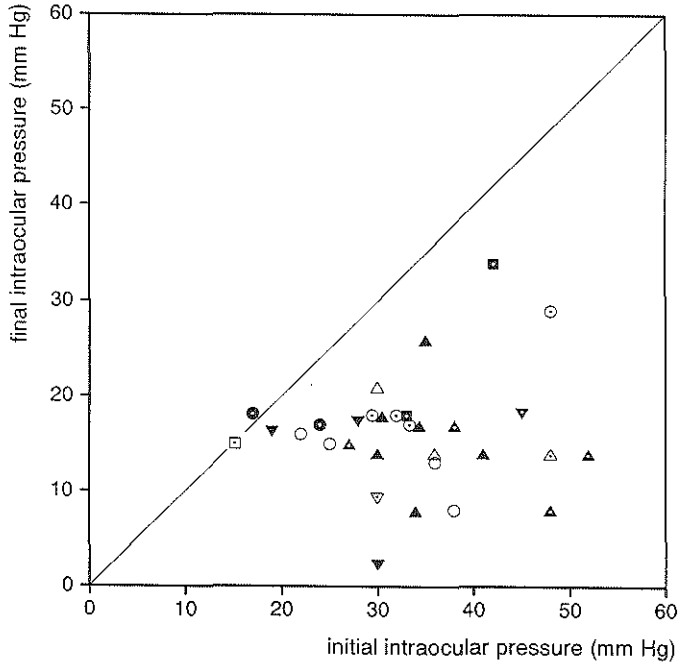

Fig. 1- Final versus initial values for intraocular pressure related to treatment. The open symbols represent eyes with suspected glaucoma treated with: medication alone (○), laser therapy (□), glaucoma surgery once (△), glaucoma surgery more than once (▽). The closed symbols represent glaucomatous eyes treated with medication alone (●), laser therapy (■), glaucoma surgery once (▲), glaucoma surgery more than once (▼). Symbols with a dot indicate the eyes that received anti-glaucoma medication at the most recent examination.

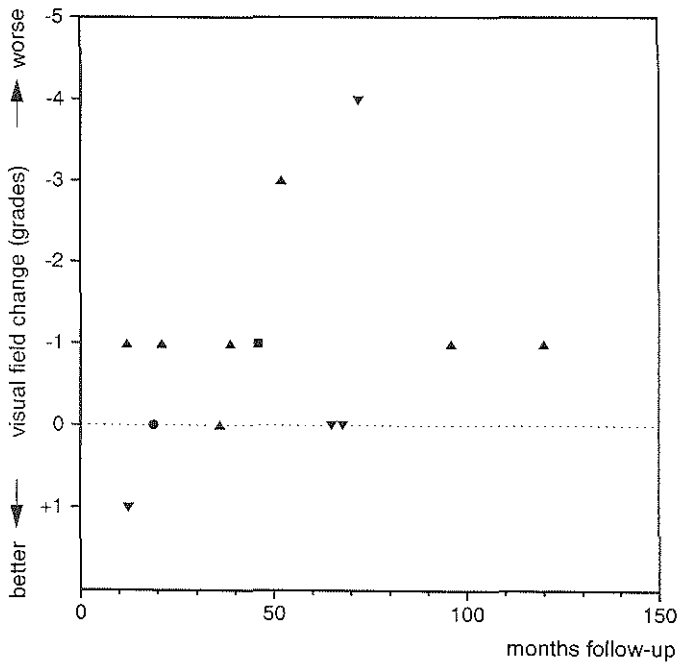

Fig. 2- Changes in visual field related to treatment and follow-up time between the first- and the last recorded perimetric test. The closed symbols represent glaucomatous eyes treated with: medication alone (●), laser therapy (■), glaucoma surgery once (▲), glaucoma surgery more than once (▼).

Results of glaucoma treatment (medical, laser and surgical therapy) were analyzed by plotting final versus initial intraocular pressure values (Fig. 1). Intraocular pressure decreased in 29 of the 31 eyes. In three eyes, final intraocular pressure remained above 21 mm Hg despite therapy (medical, laser or surgical therapy, respectively).

Of the eighteen eyes with Fuchs' heterochromic cyclitis and glaucoma, eight had visual field defects that could be classified as grade one, one eye had grade two defects, three eyes were classified as grade three, one eye had grade four defects and five eyes were classified as grade 5 (three of these five eyes were referred with grade 5 visual field defects). In five of the eighteen eyes no follow-up was recorded of perimetry. Of the 13 other glaucomatous eyes, changes in visual field due to glaucoma were related to treatment and follow-up between the first- and the last recorded perimetric test (Fig. 2). For perimetry mean follow-up was 51 months (range 12 to 120 months). An aggravation of visual field loss of one or more grades was found in eight of the 13 eyes; one eye had laser treatment and seven eyes underwent glaucoma surgery.

The increase in cup/disk ratio related to therapy is shown in Figure 3. An increase of 0.1 or more was encountered in 14 of the 31 eyes (five glaucoma suspect eyes and nine

glaucomatous eyes). Three of these 14 eyes were treated with medication alone, three eyes had laser therapy, and eight had additional glaucoma surgery.

Final versus initial values of (best) corrected visual acuity were related to treatment in Figure 4. Nineteen (61 %) of the 31 eyes had a final visual acuity of 20/40 or more, and 27 eyes had a final visual acuity of 20/80 or more. Three patients had corneal dystrophy; in two of these three patients visual acuity improved after penetrating keratoplasty. Six eyes lost more than one line of visual acuity. Progression of cataract or vitreous opacities caused this decrease in visual acuity in three eyes (one eye was treated with medication alone and two eyes with glaucoma surgery), whereas glaucoma was the main cause of visual loss in three other eyes (one eye was treated with medication alone and two eyes with glaucoma surgery).

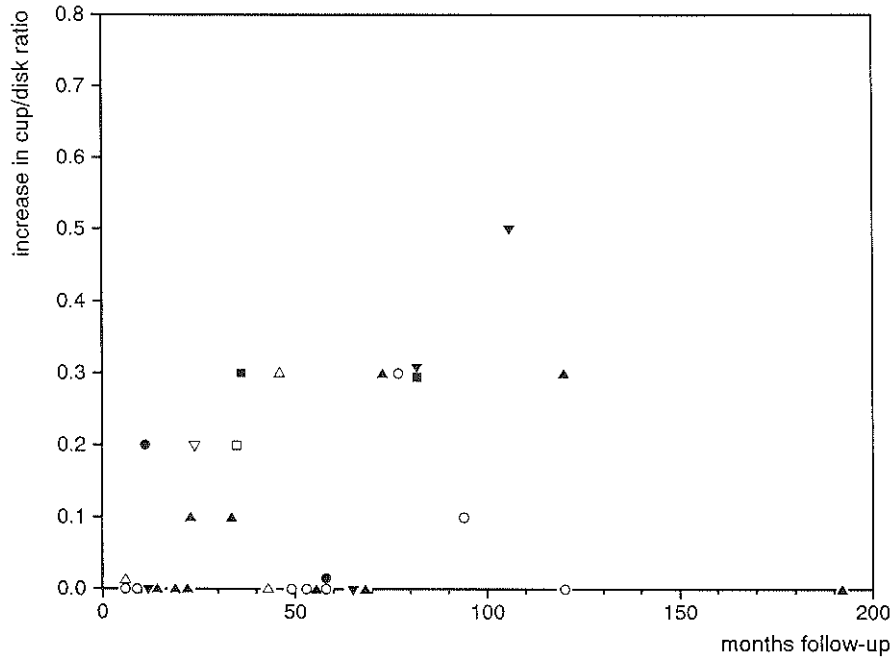

Fig. 3- Increase in cup/disk ratio related to treatment and follow-up. The open symbols represent eyes with suspected glaucoma treated with: medication alone (○), laser therapy (□), glaucoma surgery once (△), glaucoma surgery more than once (▽). The closed symbols represent glaucomatous eyes treated with medication alone (●), laser therapy (■), glaucoma surgery once (▲), glaucoma surgery more than once (▼).

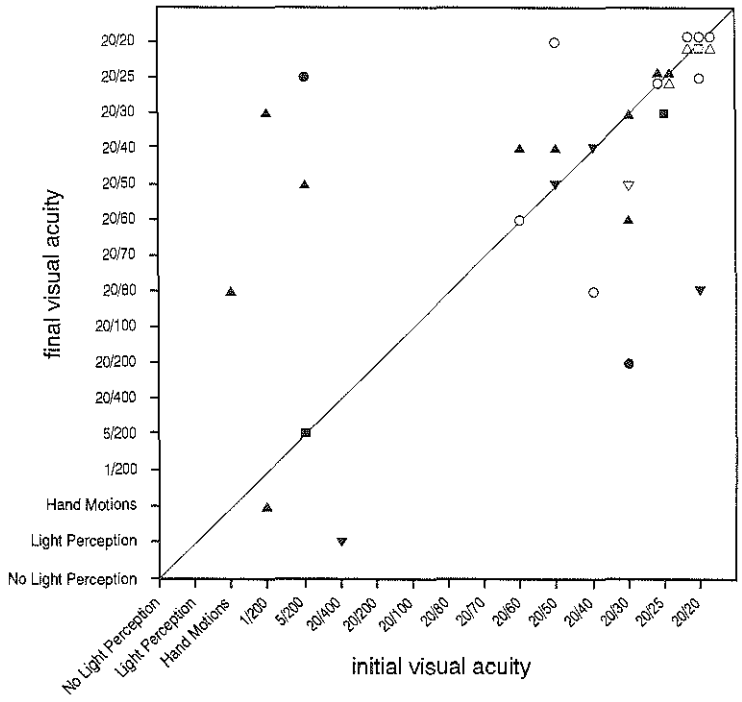

Fig. 4- Final versus initial values of (best) corrected visual acuity related to treatment. The open symbols represent eyes with suspected glaucoma treated with: medication alone (○), laser therapy (□), glaucoma surgery once (△), and glaucoma surgery more than once (▽). The closed symbols represent glaucomatous eyes treated with: medication alone (●), laser therapy (■), glaucoma surgery once (▲), and glaucoma surgery more than once (▼).

Glaucoma surgery was performed in eighteen patients with Fuchs' heterochromic cyclitis and (suspected) glaucoma. After one filtration procedure, in 13 (72 %) of the 18 patients successful (complete and qualified) control of intraocular pressure was obtained, either without medication (in eight patients) or with medication (in five patients) after a mean follow-up of 26 months (range 5 to 120 months). Three patients were reoperated once, and one patient needed two reoperations. Therefore, altogether 23 filtration operations were carried out in 18 patients. Table 2 summarizes all 23 surgical procedures, their surgical outcome, and pre-and postoperative values of intraocular pressure, visual acuity and number of anti-glaucoma medications. The specific intraocular pressure results were also determined (Fig. 5). Nine of the 23 glaucoma operations could be categorized as complete successes, seven as qualified successes, one as qualified failure and six as complete failures. Of all operations categorized as successes, mean postoperative follow-up was 31 months (range 5 to 120 months). Of the six operations that were categorized as complete failures, further glaucoma surgery was performed five times (four eyes), after a mean period of 13 months

(range 1 to 33 months), and once enucleation was recommended. In three of the four reoperated eyes success was achieved (one complete and two qualified). Thus, in 16 out of 18 patients successful control of intraocular pressure was ultimately obtained after 20 glaucoma operations.

The cumulative success rate (complete and qualified) by Kaplan-Meier analysis of the first filtration procedures is presented in Figure 6: at 33 months the probability of a successful operation is 60 %. Mean postoperative intraocular pressure (14.6 $\pm$ 3.6 mm Hg) was significantly lower (P = .0001, paired t-test) than the mean preoperative intraocular pressure (36.1 $\pm$ 11.7 mmHg) when taking the first filtration procedure of each patient into account. Also, the mean number of postoperative anti-glaucoma medications (0.6 $\pm$ 1.0) was significantly lower (P = .00001) than the mean preoperative number of medications (2.4 $\pm$ 0.8).

Postoperative complications of all 23 glaucoma operations are summarized in Table 2. Bleb inadequacy (including encapsulated bleb) was the main cause of surgical failure in six eyes. Shallow anterior chamber (n=4) or flat anterior chamber (n=2) could be adequately treated with sodium hyaluronate or a megasoft bandage lens.[38] Injections with 5-fluorouracil were discontinued when a small corneal epithelial defect occurred (three times). A small hyphema appeared in four eyes. Iris hyperaemia occurring in one patient disappeared three months after surgery. Persistent hypotonia occurred in one patient. On request of this patient, surgical intervention had been postponed and cyclocryotherapy was performed. Subsequent implantation of drainage tubes (Gonioseton) was unsuccessful, and the eye remained painful with persistent hypotonia and no useful vision (light perception); enucleation was recommended for this eye. Suprachoroidal haemorrhage, aqueous misdirection, retinal or choroidal detachment, or endophthalmitis were not encountered in this series.

None of the following factors was found in a significantly higher proportion in the glaucoma operations categorized as success than in those categorized as failure: black race, age younger than 50 years at the time of the operation, previous cataract or other intraocular surgery, aphakia or pseudophakia at the time of the operation, posterior capsule defect at the time of surgery, peripheral anterior synechiae over more than 180° preoperatively, history of failed glaucoma surgery, glaucoma surgery combined with vitrectomy or cataract extraction, and glaucoma operation with 5-fluorouracil or sodium hyaluronate. Some of the factors may have had real influences on the surgical outcome; sample sizes were too small however, to yield statistically significant differences.

Table 2- Summary clinical data operated eyes.

Patient No., Sex, Age (yrs.)	Surgical procedure	Surgical outcome	Intraocular pressure (mm Hg) pre-operative	Intraocular pressure (mm Hg) post-operative	Visual acuity pre-operative	Visual acuity post-operative	No. of anti-glaucoma medications pre-operative	No. of anti-glaucoma medications post-operative	F.Up (mos)	Peri-and postoperative complications
1 , F, 32	Trabeculectomy + urokinase	FC	28	34	20/50	20/40	2	3	21	Encapsulated bleb Hyphema
	Krupin-Denver-implant[36]	SC	34	17	20/50	20/50	3	-	44	Choroidal effusion
2 , F, 39	Scheie	FC	42	43	20/30	20/60	3	3	2	Bleb failure, hyphema
	Scheie	FC	43	38	20/60	20/100	3	1	7	Encapsulated bleb
	Trabeculectomy+ cyclocryotherapy	SQ	38	9	20/100	20/50	1	1	10	Flat anterior chamber, Bleb leak
3 , F, 56	Trabeculectomy	SC	24	14	20/30	20/30	1	-	9	-
4, M, 32	Trabeculectomy + 5-fluorouracil	SC	40	17	20/25	20/25	1	-	19	Shallow anterior chamber, hyphema
5, F, 60	Trabeculectomy + 5-fluorouracil + vitrectomy	SC	35	16	20/40	20/40	2	-	8	Corneal epithelial defect
6, F, 45	Trabeculectomy	SQ	32	15	HM	20/80‡	3	2	58†	-
7, F, 63	Trabeculectomy + 5-fluorouracil	SQ	25	8	5/200	20/50‡	3	1	5†	Corneal epithelial defect
8 , F, 43	Trabeculectomy + 5-fluorouracil	SC	33	18	20/50	20/40	3	-	10	Shallow anterior chamber

9, F, 27	Trabeculectomy + 5-fluorouracil	FQ	32	26	1/200	HM	2	-	9	Encapsulated bleb, iris prolapse into wound
10, M, 71	Trabeculectomy + 5-fluorouracil	SC	30	14	20/30	20/60‡	3	-	22†	Shallow anterior chamber, iris hyperaemia
11, F, 45	Trabeculectomy + 5-fluorouracil	SC	30	21	20/25	20/25	3	-	5	Corneal epithelial defect
12, M, 41	Trabeculectomy	SC	66	8	20/60	20/40	2	-	65	Shallow anterior chamber
13, M, 46	Trabeculectomy + 5-flourouracil	SQ	30	14	20/20	20/20	3	1	7	-
14, M, 77	Trabeculectomy	SQ	30	17	20/25	20/25	3	3	34	Hyphema
15, F, 42	Gonioseton[37]	FC	44	52	20/400	HM	2	2	1	Encapsulated bleb
	Gonioseton[37]	FC	52	2	HM	LP	2	-	8	Persistent hypotonia
16, F, 23	Trabeculectomy	FC	42	23	20/20	20/100	3	3	33	Encapsulated bleb
	Trabeculectomy	SQ	23	18	20/100	20/80	3	-	45	-
17, F, 35	Trabeculectomy	SC	42	14	20/20	20/20	2	-	40	Flat anterior chamber, goniosynechiae
18, M, 37	Scheie + cataract extraction	SQ	52	14	1/200	20/30	2	1	120	Anterior synechiae

* Surgical outcome was categorized according to Heuer et al.[35] : SC = Success Complete, SQ = Qualified Success, FQ = Qualified Failure, FC = Failure Complete, HM = Hand motions, LP = Light Perception

† Follow-up was artificially terminated due to subsequent cataract extraction or penetrating keratoplasty.

‡ After penetrating keratoplasty.

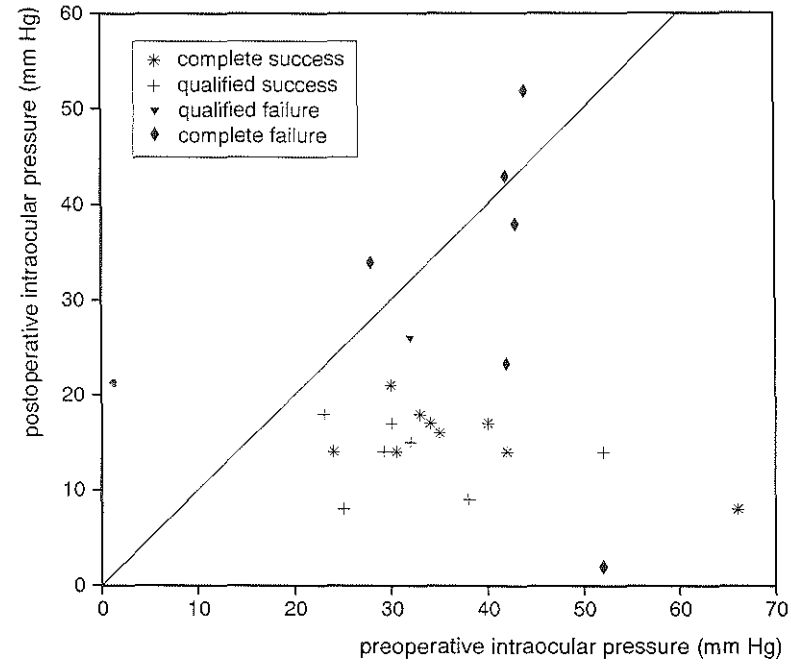

Fig. 5- Surgical outcome and specific intraocular pressure results of the 23 glaucoma operations.

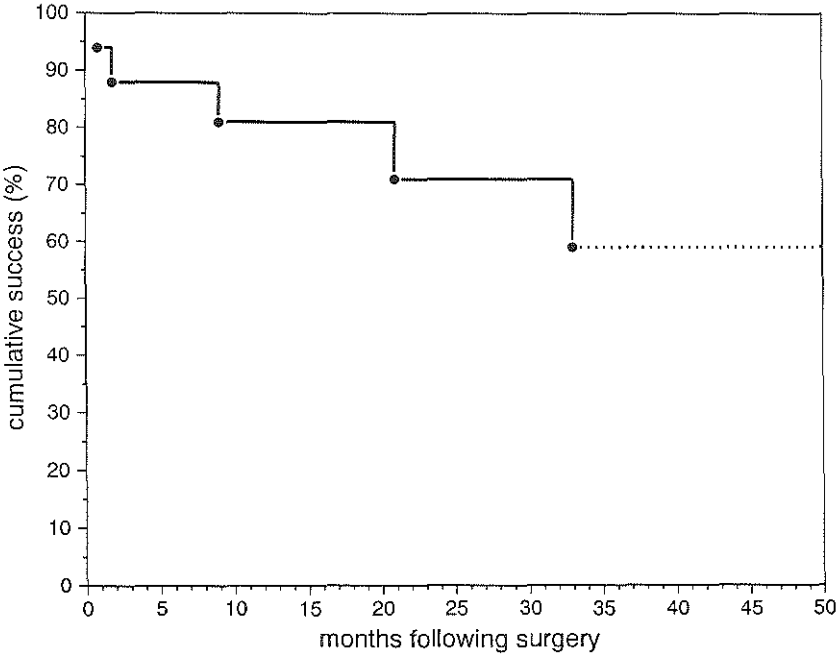

Fig. 6- Cumulative success (percent) of the first filtration procedure by Kaplan-Meier product limit analysis.

Discussion

In our series, 30 (27 %) of the 111 patients with Fuchs' heterochromic cyclitis had glaucoma or could be considered "glaucoma suspects". This percentage is somewhat higher than the study by Dernouchamps,[13] who reported a prevalence of glaucoma of 18.6% based on 550 patients and Loewenfeld and Thompson,[12] who found a prevalence of 15% based on a literature review of 1116 cases with Fuchs' heterochromic cyclitis. The higher percentage in the current series may be attributed to the fact that many of our patients were referred for glaucoma therapy and that we, in contrast with other studies,[12-15,27,28] included 13 glaucoma suspect eyes in our analysis. Moreover, we studied results after a long-term follow-up period (mean 5.9 years); therefore our results are more comparable to a study of Liesegang,[15] who reported the highest prevalence of glaucoma (59 %), after a mean follow-up period of 9.2 years. The prevalence of secondary glaucoma in Fuchs' heterochromic cyclitis in the current study was similar to a recent study on various types of chronic uveitis,[39] in which the same criteria were used.

We could not confirm previous studies that reported a (female) gender predilection,[28] a higher prevalence of bilateral involvement[24] or a higher proportion of cases in blacks[14] in glaucomatous compared to non-glaucomatous patients with Fuchs' heterochromic cyclitis.

As reported in earlier studies,[14,15] abnormalities in the chamber angle did not correlate well with the incidence and severity of glaucoma. Peripheral anterior synechiae (PAS) over more than half of the chamber angle were found in three patients; it is not clear whether they were the main cause of glaucoma in these patients. Moreover, abnormal vessels in the chamber angle may be seen in patients with Fuchs' heterochromic cyclitis with and without glaucoma.[15,26] It is not certain whether they are really pathological, as they were also found in more than one-third of 269 normal eyes.[40] Maybe these vessels are more easily visible in patients with Fuchs' heterochromic cyclitis due to depigmentation of the anterior iris stroma near the chamber angle.[12]

Whether the high incidence of post-operative glaucoma is a complication of cataract surgery[41-43] or represents the natural course[2,3,7,8] of Fuchs' heterochromic cyclitis is still not clear. Concerning (the number of) cataract procedures or postoperative complications, we could not find any significant differences between the glaucomatous and the non-glaucomatous patients with Fuchs' heterochromic cyclitis. In 12 (21 %) of the 58 eyes with Fuchs' heterochromic cyclitis that had cataract surgery, a secondary glaucoma developed postoperatively. This percentage is comparable to most of the studies on cataract surgery in patients with Fuchs' heterochromic cyclitis that reported a permanent elevation of intraocular pressure developing at some time following operation in 3 to 35 % of these eyes.[1-9,41-43] In other uveitis entities postoperative glaucoma develops in a similar percentage.[2] Since glaucoma has also been reported in 12 to 25 % [2,10-16,24,28,29] of the unoperated eyes with Fuchs' heterochromic cyclitis, the reported incidence rate following cataract surgery may actually reflect only the natural course of the disease.[2,3,7,8]

In the current study, six (10 %) of the 58 patients who underwent cataract extraction had preexisting glaucoma. Cataract surgery with or without intraocular lens implantation appeared to have no unfavourable effect on the control of glaucoma postoperatively. In general, also in eyes with pre-existing glaucoma, control of intraocular pressure is thought not to be altered by cataract extraction with or without intraocular lens implantation.[44] A filtration procedure combined with cataract surgery was successfully carried out in one of our patients. A combined procedure may be a justified procedure in these patients, because eventually all patients with Fuchs' heterochromic cyclitis need cataract removal, and a combined procedure reduces the number of surgical interventions.

Maximal medical therapy was unsuccessful in controlling intraocular pressure in 22 (73 %) of the 30 patients with Fuchs' heterochromic cyclitis and (suspected) glaucoma. Such a high percentage of failure with medical treatment confirms earlier studies,[15,27] but is in disagreement with Jones,[28] who reported that medical treatment failed in only 37 %. Jones however, provided no details on the kind of medical therapy he used. In a study on glaucoma in patients with various types of uveitis, Panek et al.[39] reported that in over 90 % of these patients, intraocular pressure was adequately controlled with medication alone, and only one out of 23 patients required filtration procedures.

After one filtration procedure, successful control of intraocular pressure ($\leq$ 21 mm Hg) was achieved in 13 (72 %) of the 18 patients with Fuchs' heterochromic cyclitis and (suspected) glaucoma after a mean follow-up of 26 months. Ultimately, success was achieved in 16 of the 18 patients (after 20 glaucoma operations). When considering only the first trabeculectomies, we achieved a success rate as high as 12/15 (80 %): seven out of eight trabeculectomies with 5-fluorouracil and five out of seven trabeculectomies without 5-fluorouracil were successful. Our success percentage is higher than that of Liesegang[15] who reported successful control of intraocular pressure in 12 (57 %) of the 21 patients with Fuchs' heterochromic cyclitis and glaucoma after one filtration procedure. Jones[28] reported satisfactory control of intraocular pressure in three out of six cases after a single procedure (mean postoperative follow-up of 27 months) and in three other cases after nine glaucoma operations. A third study[27] reported that all six surgical procedures carried out in five patients resulted in a short term hypotensive effect followed by intractable ocular hypertension. In the previously mentioned studies[15,27,28] usually trabeculectomies, but also cyclocryotherapy, cyclodialysis, combined procedures or Scheie operations were performed. However, no fibrosis inhibiting drugs were used. Two studies[15,27] provided no details on the postoperative follow-up time.

Most authors report their results on glaucoma surgery relating primarily to intraocular pressure control. It is well known however, that in 20 to 40 % of the patients with a lowering of intraocular pressure by glaucoma surgery, progression of visual field defects is not arrested.[45,46] Nine of the 16 patients with successfully controlled intraocular pressure in our study, showed a progression of visual field loss and/or had an increase in cup/disk ratio of 0.1 or more. An increase in the cup/disk ratio of 0.1 has recently been shown to

correspond with a 10 % loss of optic nerve fibers.[47] Thus, despite successful intraocular pressure control, the damage from glaucoma continued in our series of patients with Fuchs' heterochromic cyclitis.

Visual acuity results in the patients with Fuchs' heterochromic cyclitis and (suspected) glaucoma in the present series, were better than reported by Jones[28] or by Liesegang.[15] Sixteen of our 18 patients who ultimately had successful surgical control of intraocular pressure, retained a visual acuity of 20/80 or better. Four of these 16 successfully operated patients were glaucoma suspects without visual field defects. Liesegang reported poor visual acuity (less than 1/200) because of glaucoma in five of the 12 successfully operated patients.[15]

The main cause of failure in the current series of glaucoma operations was encapsulated bleb, which is in agreement with earlier findings.[15,27,28] It is well established that 5-fluorouracil inhibits bleb scarring, but the process of bleb encapsulation has been found to be less sensitive to 5-fluorouracil.[48] Moreover, although successful in seven out of eight procedures, the number of operations performed with 5-fluorouracil in the current study was too small to draw significant conclusions. The use of sodium hyaluronate also appeared to have a beneficial effect on the surgical outcome: nine out of 11 procedures were successful. This number was however, too small to yield statistical significance. In contrast with previous studies[15,27,28] we found a low incidence of peri-and postoperative intraocular haemorrhages. In view of our favourable surgical results, this finding may lend support to the hypothesis of O'Connor[1] who believed that vascular accidents may be responsible for failure of filtration surgery in patients with Fuchs' heterochromic cyclitis. Eyes that had previous unsuccessful glaucoma surgery seemed to be at higher risk for failure, as is well known from the literature.[48]

For appropriate statistical comparison of our surgical success rate with that in a matched control group of patients with other types of uveitis, our number of operated patients with Fuchs' heterochromic cyclitis was too small, due to the presence of many confounding factors (such as age, race, sex, use of various surgical techniques, number of previous intraocular procedures, and number of preoperative medications) for which matching (stratification) would be necessary. Moreover, we were unable to find a large enough matched control group of patients with uveitis who were operated in our clinic(s) in the same period, to set up a hypothesis test with enough statistical power.[49] We therefore related our surgical results only to success rates for filtration surgery in other types of uveitis reported in the literature.

The tendency to avoid filtration surgery in eyes with inflammatory glaucoma[50] may explain that there is little documentation on glaucoma surgery in this patient group. Kanski et al.[51] reported successful control of intraocular pressure after trabeculodialysis in 18 (60 %) of the 30 eyes with chronic anterior uveitis associated with juvenile rheumatoid arthritis. In a recent study on patients with various types of uveitis, ten of the 12 trabeculectomies with 5-fluorouracil were successful without intraocular pressure lowering medication.[52] Also from

our series and from a small series reported by Weinreb[53], the use of 5-fluorouracil in glaucoma surgery for uveitis patients seems promising. It is not clear whether the inhibiting effect of 5-fluorouracil on bleb scarring[48] or a possible anti-inflammatory effect of 5-fluorouracil on inflammatory mediators[52,53] may be responsible for this success. The role of other fibrosis inhibitors such as mitomycin c remains to be evaluated.

Because only few (above mentioned) studies have been published on the surgical management of secondary glaucoma in uveitis, we also compared our results with success rates of various filtration procedures (trabeculectomies with and without 5-fluorouracil and valve implants) in other high-risk situations,[35,36,53-60] such as aphakia (39 - 87 %), neovascular glaucoma (67 %), young patients (51 %), black patients (72 - 86 %) and eyes with previous unsuccessful filtration procedures (75 - 92 %). In most series approximately the same success criteria, based on intraocular pressure, were used as in our study. Our results are roughly comparable with these studies.

Our success rate (72 %) of glaucoma surgery in Fuchs' heterochromic cyclitis is somewhat lower than the success rate (75 to 90 %) reported after trabeculectomy for primary open angle glaucoma.[34,45,46,61,62] In a recent study, the success rate with initial 5-fluorouracil in trabeculectomy for uncomplicated glaucoma was even 100 %.[63] In an earlier study from our clinic, reporting on glaucoma surgery (Scheie operations and trabeculectomies) in 77 patients with primary open angle glaucoma, a success rate of 88% was achieved.[64]

As with cataract extractions in Fuchs' heterochromic cyclitis, filtration procedures with modern surgical techniques may have good results. From our series, the use of 5-fluorouracil and sodium hyaluronate seem promising. Recently, long-term topical anti-glaucoma medication have been shown to induce chronic inflammatory changes in the conjunctiva, which may enhance the risk of bleb scarring and failure of filtration surgery.[65] In view of the high failure rate with anti-glaucoma medication and the successful surgical results in the current study on Fuchs' heterochromic cyclitis, we think that earlier surgical intervention and the use of antimetabolites such as 5-fluorouracil may yield a favourable outcome of glaucoma in this patient group.

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Chapter 5

QUANTITATIVE ANALYSIS OF IRIS TRANSLUCENCY IN FUCHS' HETEROCHROMIC CYCLITIS

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Summary- We measured intraocular stray light by means of the direct compensation technique, and quantified translucency of the iris and the surrounding ocular wall by a modification of this technique, in both eyes of patients with Fuchs' heterochromic cyclitis. Intraocular stray light proved to be significantly higher in all patients with Fuchs' heterochromic cyclitis than in normal controls. Translucency of the iris and the ocular wall around it were increased in the patients with Fuchs' heterochromic cyclitis, including patients without heterochromia or with a minimal degree of iris atrophy. Quantitative analysis of translucency was used to determine iris depigmentation *in vivo* in patients with Fuchs' heterochromic cyclitis. This technique showed that the process of atrophy and depigmentation in patients with Fuchs' heterochromic cyclitis is probably not restricted to the iris, but also occurs in the surrounding ocular wall. More studies, including other uveitis groups, are necessary to investigate if this technique can be used as a diagnostic method in Fuchs' heterochromic cyclitis.

Introduction

Although the typical pattern of iris atrophy and depigmentation is an important diagnostic criterium in Fuchs' heterochromic cyclitis,[1-7] only a few investigations on Fuchs' heterochromic cyclitis have focused on the (de-)pigmentation of the iris, and these were mainly histopathologic studies.[8-12] Iridectomy specimens from patients with Fuchs' heterochromic cyclitis studied by electron microscopy showed a decreased number of melanocytes with loss of their dendritic processes and relatively few, small melanosomes in all layers of the iris.[8-10] Iris specimens from Fuchs' heterochromic cyclitis patients were

compared with those from patients with other types of chronic uveitis[10] and normal controls.[8] Evaluation of a possible loss of pigmented cells from the iris, however, is considered unreliable without a specimen of the opposite normal iris for comparison.[11,12]

Saari used infrared transillumination stereography to study the structural pattern of the iris in patients with Fuchs' heterochromic cyclitis.[13] He concluded that this technique could be used as a diagnostic method in the early stages of the disease, in which iris depigmentation is difficult to see by slit-lamp examination. The infrared photographs, however, only yield a rough estimation of the process of atrophy and depigmentation in the iris. To determine and monitor iris depigmentation *in vivo* in patients with Fuchs' heterochromic cyclitis quantitative analysis of translucency is necessary. We quantified iris translucency with a recently introduced technique, a modification of the direct compensation technique for the measurement of intraocular stray light.[14-18] With this technique it was possible to measure the fraction of light transmitted by the iris, "the iris transmission value" T_i.[19,20] We used this quantitative technique to determine the iris atrophy and depigmentation in patients with Fuchs' heterochromic cyclitis. Until now, only depigmentation of the iris has been studied in these patients. With this method it was possible to investigate whether pigment loss and atrophy also occur in the surrounding ocular wall. We quantified translucency in the involved eye and in the opposite eye of nine patients with Fuchs' heterochromic cyclitis, including patients without heterochromia and patients with a minimal degree of iris atrophy.

We found that intraocular stray light was significantly increased in patients with Fuchs' heterochromic cyclitis. Quantitative analysis of translucency showed that the process of atrophy and depigmentation in patients with Fuchs' heterochromic cyclitis is probably not restricted to the iris, but also occurs in the surrounding ocular wall.

Materials and Methods

Patient selection

Patients diagnosed as having Fuchs' heterochromic cyclitis (n = 111), who had visited the eye clinics of the Universities of Amsterdam and Rotterdam between 1980 and 1990, were invited to participate in this study if they had a corrected visual acuity of more than 10/20 and had a unilateral Fuchs' heterochromic cyclitis with a normal-appearing opposite eye. Most patients were seen on several occasions. Table 1 presents the diagnostic and entry criteria for this study.[1-7,21] As mentioned hereafter, except for translucency many other sources of increased intraocular lightscatter were present in this group of patients with Fuchs' heterochromic cyclitis (Table 1).[10,17,22-26] A large number of patients was therefore excluded from this study. Because it is known that intraocular stray light is increased in patients with cataract, in particular in the subcapsular type,[17] patients with a subcapsular cataract classified as more than grade 1, according to the Lens Opacities Classification System (LOCS),[25] were excluded from this study.

Table 1- The diagnostic/entry criteria and the exclusion criteria for this study.

Diagnostic criteria:[1-7,21]
(1) the absence of acute symptoms, like severe redness, pain or photophobia
(2) the (recorded) presence of characteristic small white stellate keratic precipitates
(3) minimal cells and flare in the anterior chamber
(4) diffuse iris stromal atrophy, with or without patchy loss of the iris pigment epithelium
(5) the absence of synechiae
(6) the (recorded) presence of cells and opacities in the anterior vitreous Heterochromia, cataract and glaucoma are not essential criteria for the diagnosis.[4,6,21]
Exclusion criteria*; patients
(1) with a subcapsular cataract[17] classified as more than grade 1, according to the Lens Opacities Classification System (LOCS)[25]
(2) who had a cataract extraction with or without an intraocular lensimplantation[23,24]
(3) who had more than 1+ vitreous opacities according to the classification system of Hogan, Kimura and Thygeson[22]
(4) who had undergone a peripheral iridectomy as part of a trabeculectomy
(5) with an intraocular pressure above 21 or a history of glaucoma[26]
(6) one patient with Fuchs' heterochromic cyclitis who had suffered from an HLA-B27 associated acute anterior uveitis in the same eye[10]

* Except for translucency, many other sources of increased intraocular lightscatter were present in the patients with Fuchs' heterochromic cyclitis.[10,17,22-26] A large number of patients was therefore excluded from this study.

Cataract surgery itself may cause damage and pigment loss of the posterior pigment epithelium.[23] Moreover, lightscatter may be enhanced after a cataract extraction with implantation of an intraocular lens.[24] Therefore, patients who had a cataract extraction with or without an intraocular lens implantation were also excluded. Since floaters in the vitreous appeared to interfere with the perception of the testfield in the stray light measurement, patients with Fuchs' heterochromic cyclitis who had more than 1+ vitreous opacities according to the classification system of Hogan, Kimura and Thygeson[22], were not included. Patients with Fuchs' heterochromic cyclitis who had undergone a peripheral iridectomy as part of a trabeculectomy were also left out of the study. Because a high intraocular pressure may give structural changes in the melanin granules of the iris pigment epithelium,[26] patients with an intraocular pressure above 21 or a history of glaucoma were excluded. Other types of uveitis may also give iris atrophy.[10] The one patient with Fuchs' heterochromic cyclitis who had suffered from an HLA-B27 associated acute anterior uveitis in the same eye was therefore excluded. Nine patients with Fuchs' heterochromic cyclitis were ultimately included

in this study. This research followed the tenets of the Declaration of Helsinki, and informed consent was obtained after the nature and the possible consequences of the study were explained to the participants. Seven patients were men and two were women; all patients were white caucasians; the mean age was 34 years (range 20 to 57 years). All patients underwent a complete ophthalmologic examination and their clinical findings are shown in Table 2.

Intraocular stray light and translucency were also determined in a control group of eleven normal subjects (mean age 33 years, range 24 to 55 years), matched for age and iris colour. Part of these experiments were performed in an earlier study.[19] One black normal subject was added to include measurement of the fraction of light transmitted by the iris in a person with a more intense iris colour. Of the controls only one eye was measured.

Iris

Iris stromal atrophy and transillumination of the pigment epithelium were graded by slit-lamp examination (Table 2). Photographs of undilated irides were obtained from both eyes of all patients and controls with the use of the Zeiss slit-lamp camera system (Carl Zeiss, Thornwood, NY) on a Kodak film (ektachrome, 200 ASA). The iris colour was graded according to the Iris Colour Classification system, described by Seddon et al.[27] This system was used because differences between grades are rather broad and mis-classification would result in a difference of not more than one grade. In the patients with Fuchs' heterochromic cyclitis the iris colour varied between grade one and three (Table 2). In the eleven normal controls it varied between grade one and four. The iris colour of the black subject was graded as five. In the patients with Fuchs' heterochromic cyclitis the degree of heterochromia was graded 0-2, 0 (no heterochromia), 1 (discrete heterochromia), 3 (evident heterochromia), by comparing the iris colour of the involved eye with the iris colour of the opposite eye.

Measurement of Intraocular Stray Light

In normal eyes the retinal light distribution caused by a point source of light can be considered to consist of two parts; a retinal image, resulting from light penetrating the pupil, and a homogeneous veil of light transmitted through the iris and the surrounding ocular wall.[19,20] Intraocular stray light is the light that the retina receives from directions that do not optically correspond to the location of the point source from which the light is coming from. As described extensively elsewhere,[15,16,19] the retinal light distribution caused by a point source of light, is described by the Point Spread Function (PSF). Intraocular stray light refers to the peripheral flanks of this PSF. Three main sources of intraocular stray light are well known: the cornea, the lens and the fundus (nonspecular reflections). Recent investigations[19] have indicated that a fourth source may be added: the translucency of the iris and the ocular wall around it. Especially at larger stray light angles, stray light was found to be higher in lightly pigmented eyes than in dark-brown eyes.[16,19]

Intraocular stray light was determined by the direct compensation technique, as described in detail earlier.[14-17,19,20] In short, a subject placed his head on a chin rest and fixed one eye on the centre of one of four white rings (the stray light source) projected on a translucent target screen. Figure 1 shows the apparatus with the target screen that was used for this test.[14-17,19,20] A diagram of the target screen is presented in Figure 2.
A Tungsten halogen lamp was used as light source. The ring flickered with a frequency of 8 Hz. The angular radius of the ring could be set to give angles (ϕ) of light incidence into the eye of 3.5, 7.0, 13.6 and 25.4 deg, as shown in Figure 3 for ϕ = 7 deg. The illuminance (E) at the eye resulting from these four rings was 10, 39, 115 and 153 lux, respectively. A testfield with a radius of 1 deg was present in the centre of the rings on the target screen. Due to light scattering within the eye, part of the flickering light from the ring reaches the fovea and the subject perceives a flicker in the testfield (his fixation point;

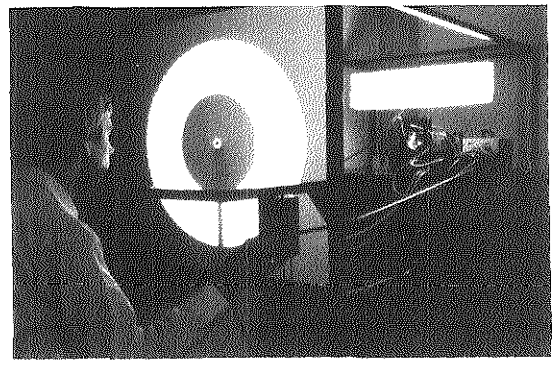

Fig. 1- The apparatus for the measurement of intraocular stray light.[14-17,19,20] Using a halogen lamp (at the back of the apparatus), a flickering white ring (the stray light source; here with ϕ = 25.4 deg) is projected on a translucent target screen. The patient with his head on a chin rest, fixates the testfield in the centre of the ring on this target screen and adjusts with a dial (on his right side) the compensating light, presented in the testfield (see Figure 2).

Figures 2 and 3). Subsequently a light was presented in this testfield flickering in counterphase with the peripheral ring. The subject had to adjust the luminance of this counterphase light (L_{tot}) to extinguish the flickering caused by stray light in the testfield (Figure 2). This luminance L_{tot} divided by E, then defines the strength of the light scattered over angle ϕ and corresponds directly to the (total) amount of intraocular stray light. L_{tot}/E has been found to vary with ϕ^{-2}.[16-19] Stray light values are expressed as so-called stray light parameters, defined by $s(\phi) = \phi^2 * L_{tot}/E$.[16-19] $\Phi^2 * L_{tot}/E$ is called the 'total' stray light parameter because it is composed of the contribution of all four stray light sources : cornea, lens, fundus, and translucency of the ocular wall. For ϕ = 25.4 deg this (total) stray light parameter is called [e].[18]

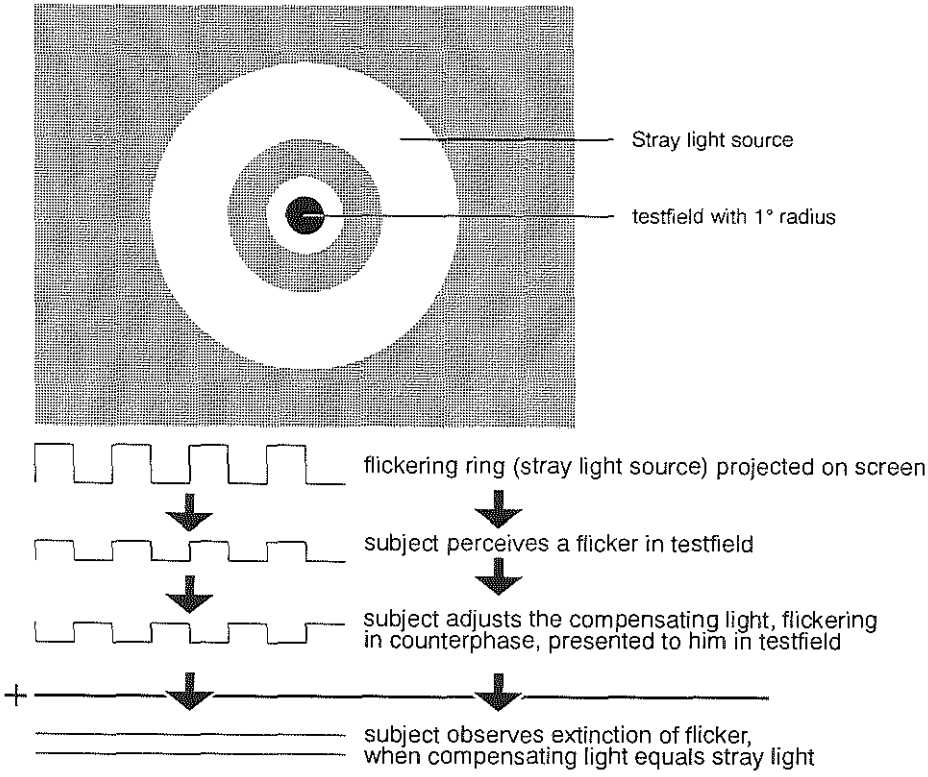

Fig. 2- Diagram of the target screen for intraocular stray light measurement[14-17,19,20] (not entire screen is depicted): a testfield with a radius of 1 deg was present in the centre of the flickering ring (stray light source; depicted here for ϕ = 7 deg) on the target screen. Due to light scattering within the eye, part of the flickering light from the ring reaches the fovea and the subject perceives a flicker in the testfield (his fixation point). Subsequently a light was presented in this testfield flickering in counterphase with the peripheral rings. The subject had to adjust the luminance of this counterphase light to extinguish the flickering due to stray light in the testfield.

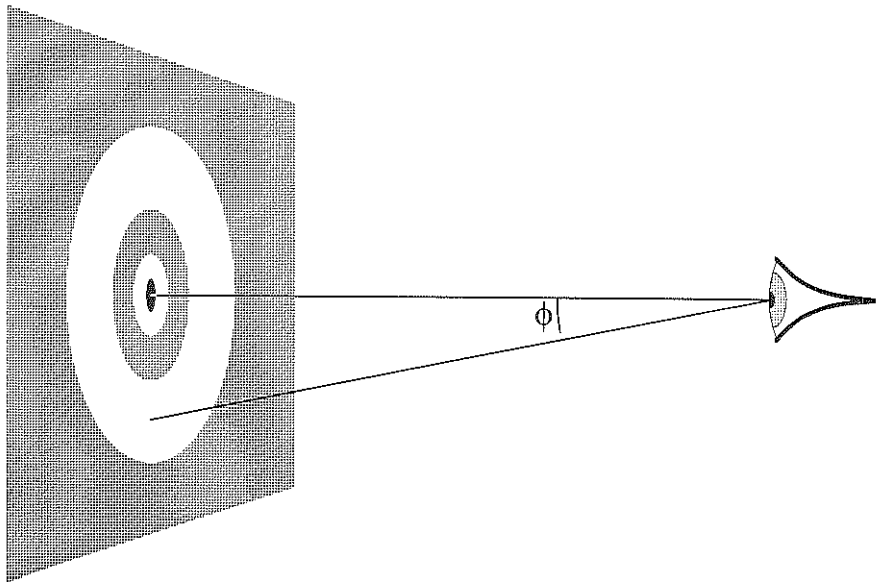

Fig. 3- The angular radius of the ring gives the angle (ϕ) of light incidence into the eye (depicted here for ϕ = 7 deg.

Measurement of Translucency

To measure the light transmitted through the ocular wall, as described in detail elsewhere,[19,20] a second apparatus was used, that was essentially the same as for measuring intraocular stray light, except for a modification of the projection system and an aperture in the (target) screen as shown in Figure 4. Now, the flickering rings were not projected on the screen, but through the aperture in the (target) screen directly on the eye. Three different flickering rings were projected on the eye (illuminance E) concentric with the pupil. Attention was paid that patients kept their eyes wide open. As a result the subject perceives a diffuse flicker (also occurring) at his fixation point (the testfield). Subsequently, a light flickering in counterphase was presented to the subject in the testfield (as in the intraocular stray light measurement). The subject had to extinguish the flicker in the testfield by adjusting this counterphase light (Figure 4). The luminance (L_{tr}) now needed to extinguish the flicker corresponds only with

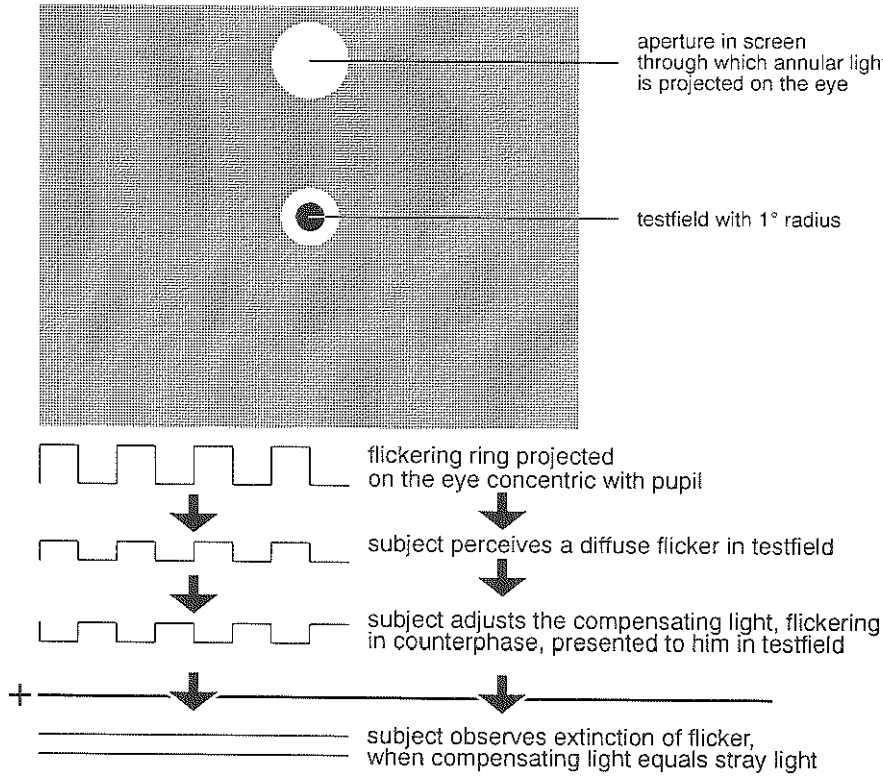

Fig. 4- Diagram of the (target) screen for the measurement of translucency[19,20] (not entire screen is depicted): Now, the flickering rings were not projected on the screen, but through the aperture in the screen directly on the eye. Three different flickering rings were projected on the eye concentric with the pupil. As a result the subject perceives a diffuse flicker at his fixation point (the testfield). Subsequently, a light flickering in counterphase was presented to the subject in the testfield, as in the intraocular stray light measurement. The subject had to extinguish the flicker in the testfield by adjusting this counterphase light.

the translucency of the part of the eye on which the flickering ring was projected. By using a ring with an inner-outer diameter of 6 to 12 mm, the contribution to the stray light parameter $s(\phi)$ of transmission through the iris [a] was measured. By using a second ring with an inner-outer diameter of 12 to 24 mm, the contribution to the stray light parameter $s(\phi)$ of transmission through the ocular wall around the iris [b] was measured, and by using a third ring with an inner-outer diameter of 6 to 24 mm, the contribution to the stray light parameter $s(\phi)$ of transmission through both the iris and the surrounding ocular wall was measured [d]. This method gives the contribution of transmission through the respective part of the ocular wall to the stray light parameter $s(\phi)$ as $\phi^2 * L_{tr} / E$. Only one angle (ϕ) of light

incidence into the eye was tested, since L_{tr}/E was found[19,20] to be more or less independent of ϕ. To calculate how much transmission contributed to the total stray light parameter for $\phi = 25.4$ deg [e], L_{tr}/E was multiplied with ($\phi^2 = 25.4^2$). For the purpose of this study we used the term "ocular wall around the iris" to indicate that part of the scleral wall that ranges from the corneoscleral limbus and extends over the major part of the ciliary body. Since the actual pupil size recorded in this study varied between 3 and 4.5 mm, an inner ring diameter of 6 mm was too large and a portion of the iris surface (around the pupil) was missed by the 6 to 12 mm and 6 to 24 mm rings. If we assume transmission to be homogeneous, the error made is proportional to this piece of iris surface missed (4 to 6 mm). The values found were therefore corrected by multiplication with these surface effects (1.19 for the 6 to 12 mm annulus and 1.04 for the 6 to 24 mm annulus), as described earlier.[19] Comparison of [d] with the mathematical sum [a] + [b] = [c] gives an impression of the experimental error. The lowermost values (found in the black subject) were in the range of instrumental stray light (around 0.1 (deg/rad)^2).

The fraction of light transmitted by the iris, T_i (iris transmission value), can be derived from [a].[19] Technical details and calculations of how we arrived at T_i were published in our earlier study[19], in which T_i was called "diffuse filter value of the iris, "dfv(iris)".

Infrared Transillumination Photographs of the Iris

Infrared transillumination photographs of both eyes from all patients with Fuchs' heterochromic cyclitis were made to localize the atrophic changes in the iris. A high intensity light from an electronic flash unit was led through an infrared transmitting filter (Kodak Wratten filter No. 87; a cut-off filter with a 10 % transmittance at 760 nm: transmitting $\lambda > 760$ nm) via glassfibre optics through the temporal side of the eye behind the plane of the iris. Photographs were taken with a Nikon F3 camera with a Micro-Nikkor lens (200 mm) with a second infrared filter on a Kodak high-speed infrared black and white film (Kodak-HIE). These photographs were used to evaluate the presence of atrophic changes in the whole iris and especially in the sphincter muscle, the pupillary margin and in the layer of the pigmented epithelium. Also the degree of atrophy was graded using the opposite eye as control, by two independent observers in a masked fashion.

Statistical analysis was performed by means of the Student's t-test. Testing was always one-sided.

Results

Intraocular Stray Light

Stray light as a function of scatter angle for all patients with Fuchs' heterochromic cyclitis and the eleven matched controls is presented in Figure 5. Mean values for the stray light parameter at the four scatter angles were further compared with mean values obtained in an earlier study[16] of 39 normal controls with blue-green eyes (iris colour grade 1 to 3), 19

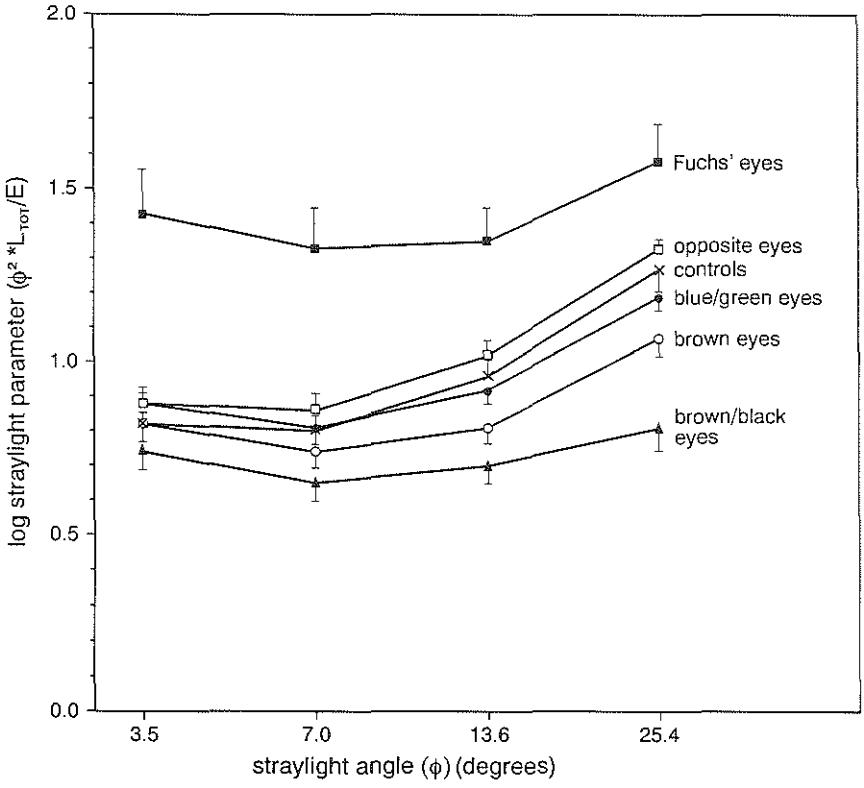

Fig. 5- The means + SEM for the log stray light parameter at the four stray light angles for the nine eyes with Fuchs' heterochromic cyclitis (closed squares), the opposite eyes of these patients (open squares), the eleven normal controls measured in this study (x), and normal controls measured in an earlier study[16] with blue/green eyes (closed circles), with brown eyes (open circles) and black controls (closed triangles). Especially at larger stray light angles stray light is higher in lightly pigmented eyes than in dark brown eyes. Mean intraocular stray light values for all angles were much higher ($P < 0.0005$) in the eyes with Fuchs' heterochromic cyclitis. Stray light was also somewhat increased in the opposite eyes of these patients compared to normal controls.

controls with brown eyes (iris colour grade 4), and 20 black controls with brown eyes (iris colour grade 5). Mean values for stray light proved to be much higher ($P < 0.0005$) for all angles in the eyes with Fuchs' heterochromic cyclitis compared to the eyes of the normal

control groups. Stray light was also somewhat higher, although not statistically significant, in the opposite eyes of these patients than in the eyes of normal controls.

Log [e], represents the (total) stray light parameter at $\phi = 25.4$ deg and corresponds to the value for intraocular stray light at this angle, as shown in Figure 5. Table 3 presents the mean $\pm$ SD for intraocular stray light in patients with Fuchs' heterochromic cyclitis and normal controls. In the eyes with Fuchs' heterochromic cyclitis mean log [e] was 1.58 $\pm$ 0.34 SD. This was significantly higher ($P < 0.025$) than in the control group of the eleven age-and iris-colour matched subjects, in which mean log [e] was 1.27 $\pm$ 0.22 SD. In eight out of nine patients, [e] in the eye with Fuchs' heterochromic cyclitis was higher than in the opposite eye of the same patient. Mean log $[e]_{(c)yclitic\ eye}/[e]_{(o)pposite\ eye}$ in the patients with Fuchs' heterochromic cyclitis was 0.25 $\pm$ 0.33 SD, which was significantly different from zero ($P < 0.05$; by paired t-test). [e] was extremely high in the eye with Fuchs' heterochromic cyclitis of case 1; it was higher than in the eye of any control. Mean log [e] in the opposite eyes of the patients with Fuchs' heterochromic cyclitis was 1.33 $\pm$ 0.08 SD, which was not significantly different from the control group.

Translucency

In Figure 6 four normal controls with different eye colours are presented. In darker eyes, values for transmission through the iris [a], transmission through the ocular wall around the iris [b], the mathematical sum [a] + [b] = [c], transmission through both the iris and the surrounding ocular wall, and the total stray light parameter [e], all decreased significantly. This is in agreement with our earlier study.[19] The values for [a] to [e] of case 3 with Fuchs' heterochromic cyclitis are presented in Figure 7. The contribution to the stray light parameter of transmission through the iris (bar [a]) was much higher in the affected eye than in the opposite eye. Especially at larger stray light angles translucency contributed significantly to the total stray light parameter, as shown in Figure 8 for case 3. The solid line represents the stray light parameter for the four stray light angles and the dashed line shows the contribution originating from transmission ([c] or [d]).[19] In case 3, the stray light parameter at 25.4 degrees; [e], was approximately 75 $(deg/rad)^2$ in the eye with Fuchs' heterochromic cyclitis and 28 $(deg/rad)^2$ in the opposite eye. Translucency contributed at this angle around 34 $(deg/rad)^2$ and 11 (deg/rad), respectively. Thus, light originating from transmission through the ocular wall was a significant part of the total amount of light penetrating the eye, especially in the eye with Fuchs' heterochromic cyclitis.

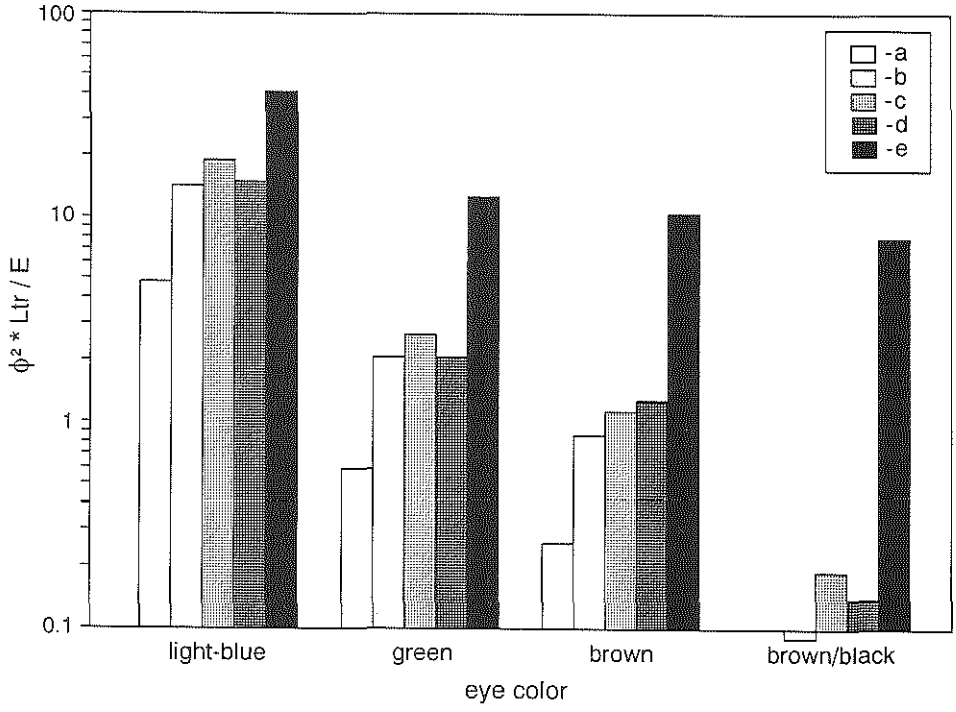

*Fig. 6- Transmission through the ocular wall in relation to pigmentation of the iris in four normal controls. From left to right bars represent for ϕ = 25.4 deg the transmission through the iris [a], the contribution to the stray light parameter of transmission through the ocular wall around the iris [b], the mathematical sum [a] + [b] = [c], the contribution to the stray light parameter of transmission through the iris and the ocular wall around it ;[d]), and the total stray light parameter [e] = ϕ^2 * L_{tot}/E for ϕ = 25.4 deg. [a] to [e] decreased significantly in darker eyes.*

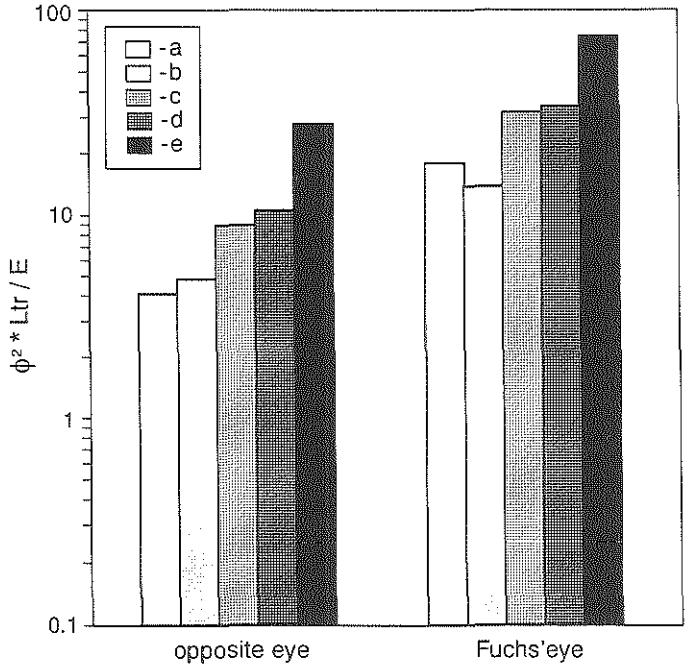

Fig. 7- Transmission through the ocular wall in both eyes of case 3. From left to right bars represent for ϕ = 25.4 deg the transmission through the iris [a], the contribution to the stray light parameter of transmission through the ocular wall around the iris [b], the mathematical sum [a] + [b] = [c], the contribution to the stray light parameter of transmission through the iris and the ocular wall around it ; [d], and the total stray light parameter [e] = $\phi^2 * L_{tot}/E$ for ϕ = 25.4 deg. All values are much higher in the eye with Fuchs' heterochromic cyclitis than in the normal eye.

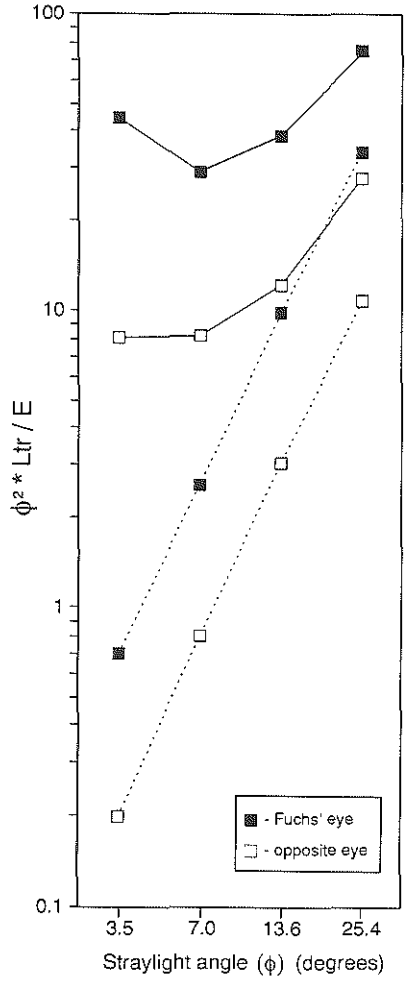

Fig. 8- The stray light parameter as function of angle for both eyes of case 3. The solid line represents the stray light parameter for the four stray light angles and the dashed line shows the part that originates from transmission.[19] Especially at larger stray light angles translucency contributes significantly to the total stray light parameter. Light originating from transmission through the ocular wall was a significant part of the total amount of light penetrating this eye, especially in the eye with Fuchs' heterochromic cyclitis.

Log [a], represents the contribution to the stray light parameter of transmission through the iris. In the eyes with Fuchs' heterochromic cyclitis the mean value for log [a] was 0.89 $\pm$ 0.40 SD, which was significantly higher ($P < 0.005$) than in the control group, in which mean log [a] was 0.24 $\pm$ 0.46 SD. In all nine patients, [a] in the eye with Fuchs' heterochromic cyclitis was higher than in the opposite eye of the same patient (Table 2). Mean log $[a]_c/[a]_o$ in the patients with Fuchs' heterochromic cyclitis was 0.61 $\pm$ 0.29 SD, which was significantly different from zero ($P < 0.0005$; by paired t-test). In the opposite eyes of the patients with Fuchs' heterochromic cyclitis, the mean value for log [a] was 0.27 $\pm$ 0.35 SD. This was not significantly different from the control group.

Table 2- Clinical data, translucency data and scores of the infrared photographs of the eyes with Fuchs' heterochromic cyclitis (compared to the opposite eyes of the same patient).

Case	KP*	Cells/ flare aqueous*	Lens†	Vitreous*	Iris stromal atrophy‡	Iris PE atrophy‡	Grade iris colour FHC / opposite eye§	Log $[a]_c/[a]_o$	Log $[b]_c/[b]_o$	T_{ic}/T_{io}	T_i/ 0.00006‖	Infrared¶
1	1	1-2	Pl	0	1	0	2 / 3	0.88	0.68	0.0046	331	5
2	2	2	Pl	0	2	1	1 / 2	0.92	0.42	0.0051	118	7
3	2	1	0	0	1	0	1 / 1	0.64	0.45	0.0027	145	5
4	1	1	0	0	1	0	1 / 1	0.22	0.68	0.0010	37	3
5	3	1	0	0	2	0	1 / 2	0.96	0.21	0.0056	39	8
6	0	1-2	0	0	1	0	1 / 2	0.58	0.17	0.0023	36	2
7	1	1	0	1+	2	0	3 / 3	0.34	0.03	0.0013	35	4
8	1	1	Pl	1+	1	0	1 / 1	0.24	0.13	0.0011	60	5
9	2	1	Pl	1+	2	0	1 / 1	0.83	0.67	0.0032	101	4

PE = Pigment Epithelium, KP = Keratic Precipitates, FHC = eye with Fuchs' heterochromic cyclitis

* Graded according to Hogan, Kimura, Thygeson[22]

† Graded according the Lens Opacities Classification System, described by Chylack et al.[25]

‡ Iris stromal atrophy and transillumination of the pigment epithelium were graded by slit-lamp examination; 0 (no atrophy) - 1 (minimal atrophy) - 2 (moderate atrophy) - 3 (severe atrophy).

§ Iris colour was graded 1-5 with colour photographs by the Iris Colour Classification System, described by Seddon et al.[27]

$[a]_c/[a]_o$ Ratio of the contribution to the stray light parameter of transmission through the iris between the (c)yclitic eye and the (o)pposite eye.

$[b]_c/[b]_o$ Ratio of the contribution to the stray light parameter of transmission through the ocular wall around the iris between the (c)yclitic eye and the (o)pposite eye.

T_{ic}/T_{io} Ratio of the iris transmission value (the fraction of light that is transmitted by the iris) between the (c)yclitic eye and the (o)pposite eye.

‖ T_i of the cyclitic eye as compared to T_i of a black normal subject (T_i = 0.00006).

¶ Infrared transillumination photographs: (total) score of the degree of atrophy of the iris of the cyclitic eye compared to the opposite eye.

Log [b], represents the contribution to the stray light parameter of transmission through the ocular wall around the iris. In the eyes with Fuchs' heterochromic cyclitis the mean value for log [b] was 0.83 ± 0.31 SD. This was not significantly different from controls, in which mean log [b] was 0.56 ± 0.43 SD. In all nine patients, [b] in the eye with Fuchs' heterochromic cyclitis was higher than in the opposite eye of the same patient (Table 2). Mean log $[b]_c/[b]_o$ in the patients with Fuchs' heterochromic cyclitis was 0.32 ± 0.24 SD, which was significantly different from zero ($P < 0.0025$; paired t-test). In the opposite eyes of the patients, the mean value for log [b] was 0.50 ± 0.33 SD. This was not significantly different from controls.

Table 3 presents the mean ± SD for translucency in patients with Fuchs' heterochromic cyclitis and normal controls. Table 2 presents clinical data on iris(de-) pigmentation and translucency data in the cyclitic eye (compared to the opposite eye) of the patients with Fuchs' heterochromic cyclitis.

Table 3- Mean ± SD for intraocular stray light and transmission through the ocular wall in the patients with Fuchs' heterochromic cyclitis and normal controls.

	Eyes with FHC	Opposite eyes	Normal control eyes
Log [a]	0.89 ± 0.40	0.27 ± 0.35	0.24 ± 0.46
Log [b]	0.83 ± 0.31	0.50 ± 0.33	0.56 ± 0.43
Log [c]	1.17 ± 0.34	0.72 ± 0.32	0.74 ± 0.43
Log [d]	1.12 ± 0.38	0.76 ± 0.31	0.71 ± 0.41
Log [e]	1.58 ± 0.34	1.33 ± 0.08	1.27 ± 0.22
Log [a]/[b]*	0.06 ± 0.23	-0.23 ± 0.22	-0.32 ± 0.17
T_i†	0.00682 ± 0.00642	0.00146 ± 0.00093	0.00155 ± 0.00118
$T_i/0.00006$‡	110 ± 103	24 ± 15	25 ± 19

FHC = Fuchs' heterochromic cyclitis
[a] contribution to the stray light parameter of transmission through the iris.
[b] contribution to the stray light parameter of transmission through the ocular wall around the iris.
[c] mathematical sum [a] + [b].
[d] contribution to the stray light parameter of transmission through the iris and the ocular wall around it.
[e] total stray light parameter ($\phi 2 * L_{tot}/E$) for ϕ = 25.4 deg.
* the ratio between the contribution to the stray light parameter of transmission through the iris [a], and the transmission through the ocular wall around the iris.
† T_i (iris transmission value); the fraction of light that is transmitted by the iris.
‡ T_i as compared to T_i of a black normal subject (T_i = 0.00006).

In an earlier study, it was found that in the eyes of normal controls [a], the contribution to the stray light parameter of transmission through the iris, was always less than [b], the value for the transmission through the ocular wall around the iris (log [a]/[b] < 0).[19] This was confirmed in the current study, in which the mean value for log [a]/[b] was -0.32 ±

0.17 SD in the eleven controls. [a]/[b] did not correlate with the colour of the iris. In the eyes with Fuchs' heterochromic cyclitis, the mean value for log [a]/[b] was significantly higher ($P < 0.0005$) ; 0.06 ± 0.23 SD. In the opposite eyes of the patients with Fuchs' heterochromic cyclitis, mean log [a]/[b] was -0.23 ± 0.22 SD. This value was not significantly different from that for the control group.

The 'iris transmission value'; T_i, the fraction of light transmitted by the iris, was derived from [a].[19] We calculated the ratio between T_i of the cyclitic eye and T_i of the opposite eye in Table 2. Since the T_i is related to the amount of pigment granules present in the iris,[19] we also measured the T_i in this black normal subject with a large amount of iris pigment. We compared the T_i of patients and controls to the T_i of this black subject, to see how much more light was transmitted through the iris of white patients and controls than through the heavily pigmented iris of a black subject (Tables 2 and 3). In the eyes with Fuchs' heterochromic cyclitis the T_i was up to 330 times higher (Table 2), and in the opposite eyes it was up to 50 times higher than in this darkest-eyed black subject, who had a T_i of 0.00006. The lightest-eyed control had a T_i that was almost 60 times higher than this black subject. To study the relationship with iris colour in more detail, values of the T_i were plotted as a function of eye colour (Figure 9). T_i was higher in the eye with Fuchs' heterochromic cyclitis of six patients (cases 1, 2, 3, 7, 8 and 9) than in controls with a similar eye colour. Also in three of the opposite eyes (cases 1, 2, and 7) T_i appeared higher than in controls with a similar eye colour.

Infrared Transillumination Photographs, Clinical Findings

Of the infrared transillumination photographs, the degree of atrophic changes in the iris of the eye with Fuchs' heterochromic cyclitis was scored by using the opposite eye of the same patient as control. The degree of atrophy of the anterior surface, the sphincter muscle, the pupillary margin and the pigmented epithelium were scored separately, 0 (no atrophy) to 3 (severe atrophy), and the total score per patient is presented in Table 2. In all cases atrophy of the anterior surface of the iris was seen. In case 2 pigment clumps were seen on the anterior surface (Figure 10). The sphincter muscle was involved in the atrophic process in all cases. Atrophy of the iris at the pupillary margin was seen in all patients, except for case 6. The pigmented epithelium was atrophic in five patients (cases 2, 3, 5, 7, and 8). A moderate atrophy with a typical moth-eaten appearance of the pigmented epithelium was found in case 5.

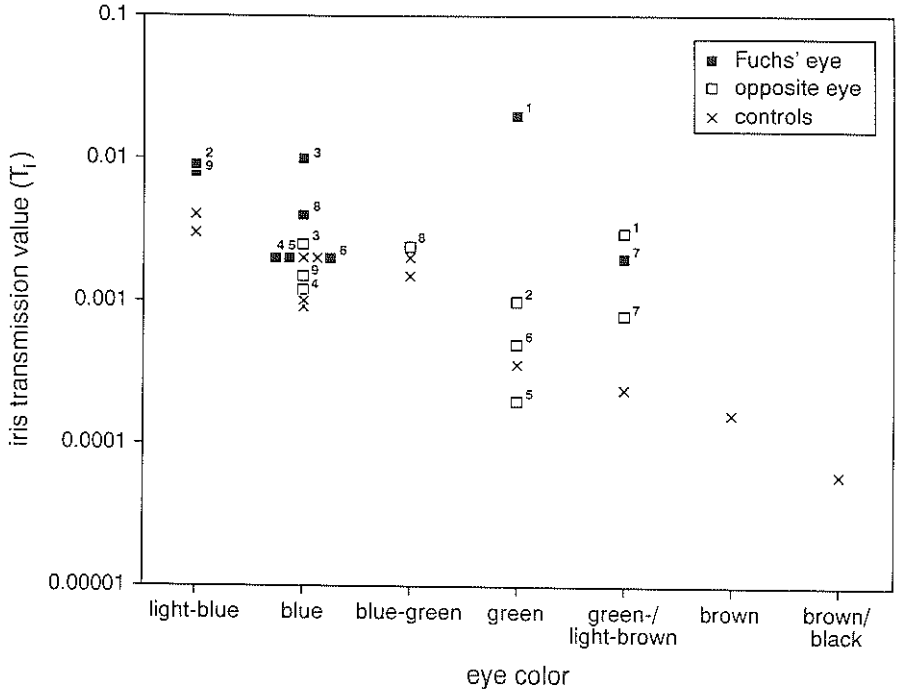

Fig. 9- The T_i (iris transmission value), the fraction of light that is transmitted by the iris, of patients and controls plotted for seven different eye colours. T_i was higher in the eye with Fuchs' heterochromic cyclitis (closed squares) of six patients (cases 1, 2, 3, 7, 8 and 9) than in controls (plus) with a similar eye colour. Also in three of the opposite eyes (open squares; cases 1, 2, and 7) T_i appeared higher than in controls with a similar eye colour.

Results of the infrared transillumination photographs corresponded well with the ratio of [a], [b] and T_i between the eye with Fuchs' heterochromic cyclitis and the opposite eye of the same patient (Table 2).

Although two patients (cases 3 and 4) had no heterochromia, our translucency measurements showed that in both cases T_i was higher in the eye with Fuchs' heterochromic cyclitis than in the normal opposite of the same patient (Fig. 9). In five patients (cases 1, 3, 4, 6 and 8) only minimal iris stromal atrophy and no atrophy of the posterior pigment epithelium could be detected by slit-lamp examination in the eye with Fuchs' heterochromic cyclitis. In all cases we measured a higher value for T_i in the eye with Fuchs' heterochromic cyclitis than in the opposite eye (Table 2 and Figure 9). Two patients (cases 4 and 5) were diagnosed as having their Fuchs' heterochromic cyclitis diagnosed less than one year earlier. In both patients T_i was higher in the eye with Fuchs' heterochromic cyclitis than in the opposite eye.

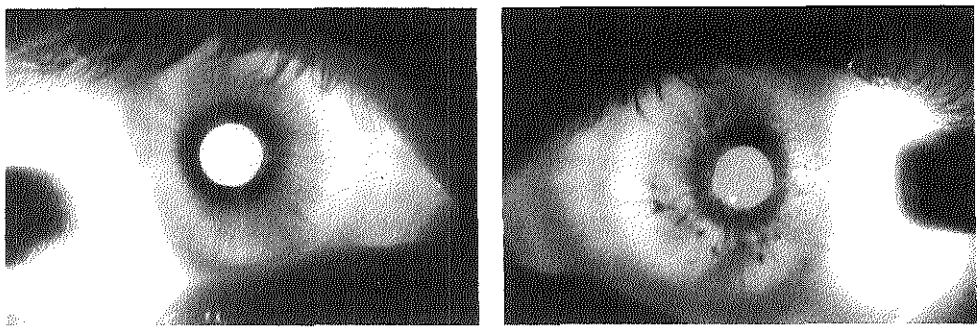

Fig. 10- Infrared transillumination photograph of the iris of case 2. In the left eye with Fuchs' heterochromic cyclitis (the right eye is the normal eye), the anterior surface, the sphincter muscle, the pupillary margin, and the pigmented epithelium of the iris show a moderate atrophy. Pigment clumps are present on the anterior surface, and the pigmented epithelium shows a "moth eaten appearance".

Discussion

This study shows that intraocular stray light was much higher in the eyes with Fuchs' heterochromic cyclitis than in the eyes of any of the controls measured in the current study or in our earlier studies.[16,19] Early changes in the lens or minimal vitreous opacities, not detectable by slit-lamp examination, may have caused the high stray light values at smaller angles (3.5 and 7.0 deg). At larger stray light angles, translucency of the iris and the ocular wall around it have probably played an important role in increasing the stray light values. Also in older normal subjects without eye pathology and with clear lenses as determined by slit-lamp examination, intraocular stray light was found to be increased.[16] This age-related increase in stray light is probably not only lenticular of origin, but may also be influenced by pigmentary changes.[16] It has previously been demonstrated that the concentration of melanin in the eye decreases with age, and this decrease was most marked in the eyes of whites after age 50.[28,29] Only one older patient with Fuchs' heterochromic cyclitis (57 years) was included in this study, together with one age-matched control. Values for the total stray light parameter and translucency in this case were not different from values obtained in younger patients and controls.

A technique of quantitative analysis of translucency was used to determine iris depigmentation in patients with Fuchs' heterochromic cyclitis. This technique is the first method to quantify the degree of atrophy and depigmentation of the iris *in vivo* in these patients. An advantage of this method is that the opposite eye can serve as a control. A specimen of the opposite eye was never available in the histopathologic studies on the iris of patients with Fuchs' heterochromic cyclitis. Moreover, any loss of pigment cells in these

histopathologic studies could have been caused by artifact or surgical trauma.[11,12] Other authors have quantified iris translucency in albinism.[30] The technique that was used however, only roughly estimated iris translucency and small increases in translucency could not be detected.

With our technique quantitative information can be obtained about the amount of pigment granules present in a layer, i.e. the iris or the surrounding ocular wall. The amount of pigment granules present in a layer is related to the fraction of light transmitted by this layer, the transmission value (T). Suppose that a fraction of 0.01 (1 %) of light falling on a pigmented layer is transmitted. When this light penetrates a second layer with the same amount of pigment granules, a fraction (T) of $0.01 * 0.01 = (0.01)^2 = 0.0001$ of the light remains. From this simple model it can be seen that the amount of pigment granules present in a layer (i.e. the iris), is expressed as the power in the transmission value:

$$T = c^n$$

where n is the amount of melanosomes and c is a constant equal for all subjects. When the highest transmission value of the iris of the black subject ($T_i = 0.00006 = c^{n1}$) is compared with the transmission value of the iris of the lightest-(blue)eyed control ($T_i = 0.00402 = c^{n2}$) a difference in the amount of pigment granules results of:

$$\frac{\text{Log } c^{n1}}{\text{Log } c^{n2}} = \frac{n1}{n2} = \frac{\text{Log } 0.00006}{\text{Log } 0.00402} = \frac{-4.2}{-2.4} = 1.75$$

From this calculation it can be seen that small differences in the amount of pigmentation result in large differences in the T (transmission value). Thus our method is thus very sensitive and we were able to measure large differences among various eye colours. This is in contrast with Menon et al.[31], who could not find a significant difference between light and dark eyes by determining the melanin concentration of the iris.

Translucency in the eye with Fuchs' heterochromic cyclitis was not only increased in the iris, but also in the surrounding ocular wall, as compared to the opposite eye. This suggests that the process of atrophy and depigmentation in Fuchs' heterochromic cyclitis is not restricted to the iris. The rings (with an outer diameter of 24 mm) that were used to measure translucency of "the ocular wall around the iris", projected light on the scleral wall ranging from the corneoscleral limbus and extending over the major part of the ciliary body. One can imagine that depigmentation of the ciliary body in the patients with Fuchs' heterochromic cyclitis may have played a role in increasing translucency values of "the ocular wall around the iris".

Translucency was found to be higher in the eyes with Fuchs' heterochromic cyclitis than in normal eyes with a similar colour. This difference may be attributed to the fact that the atrophic process in the iris of patients with Fuchs' heterochromic cyclitis, not only causes depigmentation of the iris stroma and anterior border layer, resulting in a change in the colour of the eye, but also causes a depigmentation of the posterior pigment epithelium of

the iris. An unexpected finding was the fact that translucency was increased in some of the opposite eyes, when compared with normal controls with a similar iris colour. Only one earlier study reported abnormal findings in the opposite eye of patients with Fuchs' heterochromic cyclitis; Ward and Hart found an increased outflow resistance in ten out of 16 uninvolved opposite eyes.[32]

In addition to translucency of the iris and the surrounding ocular wall, fundal reflections may contribute to the pigmentation related differences in the stray light parameter.[19] Iris pigmentation correlates directly with choroidal pigmentation.[33] Moreover, melanosomes of the anterior border and stroma of the iris, are embryologically similar to choroidal melanosomes.[7,9] Depigmentation of the choroid or a difference in fundal pigmentation between the two eyes, has never been reported in Fuchs' heterochromic cyclitis. Although two of our patients with Fuchs' heterochromic cyclitis had chorioretinal scars, no apparent difference in pigmentation between the two fundi was observed.

The infrared transillumination technique was found to be useful in evaluating disease processes that affect the iris pigment epithelium.[34] Infrared instead of white light was used because it penetrates best in the eye; melanin has an absorption spectrum with the least absorption and the greatest transmittance in the infrared region of light.[30] In our study, this technique enhanced visualization of existing posterior pigment epithelium defects and revealed defects not noted by conventional slit-lamp examination (retro-illumination). Moreover, in patients with minimal stromal atrophy noted by slitlamp examination, we could detect changes in the structural pattern of the iris on the infrared transillumination photographs by comparing the eye with Fuchs' heterochromic cyclitis with the opposite eye. Such a comparison can only be made when the same exposure time is used for both eyes. Our results corresponded well to those obtained by Saari et al.[13]

To exclude other sources of increased intraocular stray light in patients with Fuchs' heterochromic cyclitis, we used many selection criteria. Since cataract and vitreous opacities are found in almost 80 % of the patients with Fuchs' heterochromic cyclitis,[1-7,21] it was difficult to fulfil these criteria. At an early stage of the disease cataract has not yet developed and minimal vitreous opacities are present. At this time, iris changes are usually difficult to detect by slitlamp examination. In such an early stage, we measured differences in translucency between the cyclitic eye and the opposite eye. Also in patients with Fuchs' heterochromic cyclitis without heterochromia or with a minimal degree of iris atrophy, translucency values were higher in the cyclitic eye than in the opposite eye.

The infrared photographs yield only a rough estimation of the process of atrophy and depigmentation in the iris. To determine and monitor iris depigmentation *in vivo* in patients with Fuchs' heterochromic cyclitis quantitative analysis of translucency is necessary. Using this technique, we found not only depigmentation of the iris, but also depigmentation of the ocular wall around the iris in these patients. Differences in translucency were also measured in paired eyes of patients with Fuchs' heterochromic cyclitis without heterochromia or with a minimal degree of iris atrophy. More studies, including other uveitis groups, are necessary

to investigate if this technique can be used as a diagnostic method in patients with Fuchs' heterochromic cyclitis. Furthermore, quantitative analysis of translucency may be applicable in the evaluation of iris defects after cataract extraction in senile cataract, in albinism or in the pigmentary dispersion syndrome.

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Chapter 6

FUCHS' HETEROCHROMIC CYCLITIS AND RETINAL VASCULAR ABNORMALITIES IN PROGRESSIVE HEMIFACIAL ATROPHY

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Summary- We report a case of progressive hemifacial atrophy with a combination of ipsilateral Fuchs' heterochromic cyclitis and retinal vascular abnormalities. Recently, evidence was found for a neurovascular defect in hemifacial atrophy. Our case not only supports the (clinical) association between Fuchs' heterochromic cyclitis and hemifacial atrophy, but the retinal vascular abnormalities found in this patient add further support to the existence of a neurovascular defect. These findings and our short review of the literature point to the hypothesis of a common sympathetic defect, implicated in the etiology of both Fuchs' heterochromic cyclitis and progressive hemifacial atrophy. One has to keep in mind however, that Fuchs' heterochromic cyclitis has been reported in association with other diseases. It seems likely that although Fuchs' heterochromic cyclitis is a single clinical entity, it may have more than one cause.

Introduction

Hemifacial atrophy (Parry Romberg syndrome) was first described by Parry in 1825.[1] A more detailed description of this syndrome was made by Romberg in 1846, who distinguished it from the congenital non-progressive form of this disorder.[2] Hemifacial atrophy is a rare condition of unknown etiology, characterized by a slowly progressive atrophy of one side of the face, primarily involving skin, subcutaneous fat and muscles. The onset of the disease usually occurs in the first two decades of life. If the onset is before the age of ten years, the bone is also involved, resulting in a severe facial deformity.[3] In 7% of the cases the ipsilateral limbs and trunk are involved and occasionally the syndrome is bilateral.[4-6] Females are more often affected than males in a ratio of 3:2.[4] Progression of this disease occurs more rapidly in the first two to ten years and it may stabilize at any age.[7]

Many hypotheses have been put forward to explain the etiology of progressive hemifacial atrophy, which is still unknown. A relationship with either localized scleroderma,

trauma, infection, an autoimmune disorder, a trigeminal neurovasculitis, heredodegenerative factors or a defect of the sympathetic nervous system have been suggested as possible causes of this disease.[3,5,6,8,9] Ocular involvement in hemifacial atrophy occurs in up to 40% of cases.[10] Most of the ophthalmologic conditions appearing in hemifacial atrophy have been described in single case reports.

We describe a patient with progressive hemifacial atrophy who developed the clinical features typical of Fuchs' heterochromic cyclitis. In addition, ipsilateral retinal vascular abnormalities were present in the fundus of this same patient. This combination has not been reported before in the literature. Our case not only supports the association between Fuchs' heterochromic cyclitis and hemifacial atrophy, but the retinal vascular abnormalities found in this patient add further support to recent evidence of a neurovascular defect in progressive hemifacial atrophy.

Case Report

A 28-year-old caucasian woman with a previous diagnosis of a right-sided progressive hemifacial atrophy was referred to us several years ago, because of visual complaints of the right eye. The process of facial atrophy had started when she was 19 years old. Because of this late onset there was no bone- and only slight cartilage-involvement. The skin, subcutaneous fat and muscles however, were severely affected and an obvious facial asymmetry was visible (Fig 1).

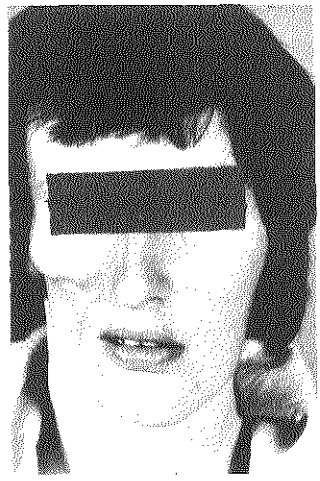

Fig. 1- Conspicuous facial asymmetry in a patient with right-sided progressive hemifacial atrophy, Fuchs' heterochromic cyclitis and retinal vascular abnormalities of the right eye.

On examination an enophthalmos and thinning of the eyebrow were noted on the right side. Best visual acuity was R.E. 10/20 and L.E. 20/20. The pupil of the right eye was larger and it showed a delayed pupillary reaction to light. In the right eye small translucent keratic precipitates scattered on the entire endothelium and minimal aqueous flare and cells were seen. Diffuse iris atrophy and a discrete heterochromia were noted. No posterior synechiae were present. The lens was clear and in the anterior vitreous fine dust-like opacities were

present. On the basis of these characteristic findings the diagnosis of Fuchs' heterochromic cyclitis was made. On fundus examination a haemorrhage above the macula along the superotemporal artery and exudates in the upper nasal quadrant of the macula were seen (Fig 2). Fluorescein angiographic studies revealed the presence of macro-aneurysms of the superotemporal artery with leakage in the direction of the macula (Fig 3). Laser coagulation was performed to decrease this leakage. In the three years that followed, the keratic precipitates and minimal aqueous chamber reaction remained unaltered. The haemorrhages and exudates diminished after repeated lasercoagulation.

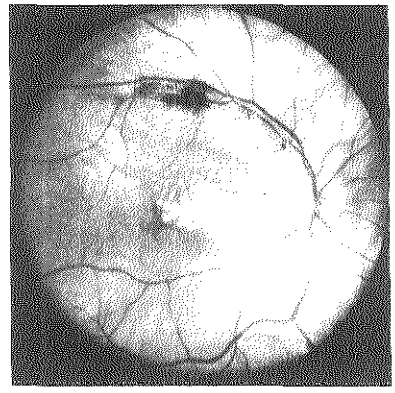

Fig. 2- Fundus photograph of the right eye showing haemorrhage (arrow) and macro-aneurysms (arrowheads) along the superotemporal artery, and exudates in the upper nasal quadrant of the macula.

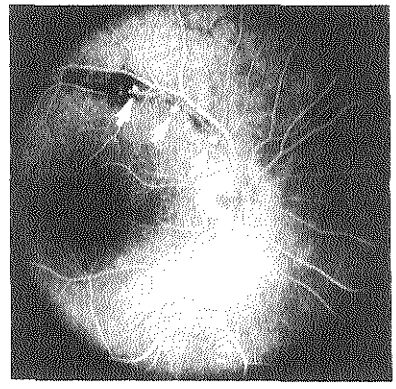

Fig. 3- Corresponding fluorescein angiogram showing macro-aneurysms (arrows) of the superotemporal artery.

Discussion

The combination of Fuchs' heterochromic cyclitis and retinal vascular abnormalities as found in our patient has, to our knowledge, not been reported before in hemifacial atrophy. Recently Gass et al. were the first to describe four cases of hemifacial atrophy with similar retinal vascular abnormalities.[11] In one of their patients a mild cellular reaction in the anterior chamber and vitreous was noted. A second patient had segmental atrophy of the iris. No other anterior segment abnormalities were described. In our patient however, in addition to the retinal vascular defects, anterior segment findings typical of Fuchs' heterochromic cyclitis were found: small translucent keratic precipitates scattered on the entire endothelium, minimal aqueous flare and cells, diffuse iris atrophy, discrete heterochromia, fine opacities in the anterior vitreous and no posterior synechiae. Complicated cataract or glaucoma had not (yet) developed.

Fuchs' heterochromic cyclitis was first considered to be associated with hemifacial atrophy because both diseases were said to be part of the Status Dysraphicus[12]. Sugar and Banks reviewed the 13 cases of Fuchs' heterochromic cyclitis in hemifacial atrophy reported since 1913 and added another case from their own practice. They suggested that both diseases may result from neurovascular or neurotrophic changes, caused by disturbances of the sympathetic nervous system.[13] Loewenfeld and Thompson[14] objected that the majority of descriptions of Fuchs' heterochromic cyclitis found in cases with hemifacial atrophy were not typical: there were unusual (pigmented) corneal precipitates, there was no iris atrophy or heterochromia and in some cases posterior synechiae were found. In our patient however, the typical features of Fuchs' heterochromic cyclitis were present, as mentioned above. Despite the arguments put forward by Loewenfeld and Thompson[14] in their extensive review to reject the association between Fuchs' heterochromic cyclitis and hemifacial atrophy, and the hypothesis of a sympathetic defect implicated in the etiology of both diseases, many authors[15-21] still support this theory put forward by Sugar and Banks.[13]

Moss and Crikelair provided evidence for this sympathetic hypothesis by demonstrating hemifacial atrophy after unilateral sympathectomy in young rats.[15] Pupillary changes, Horner's syndrome and heterochromia are often reported in patients with hemifacial atrophy, and are all signs of an impaired sympathetic nervous system.[16]

In 1953 a case was described in which Horner's syndrome and Fuchs' heterochromic cyclitis developed consecutively in the same eye after a stellate ganglionectomy.[17] Recently, five patients with unilateral Fuchs' heterochromic cyclitis and ipsilateral Horner's syndrome were reported.[18] Electron microscopic studies on Fuchs' heterochromic cyclitis have suggested that the hypochromia may result from a defective melanin production due to abnormal adrenergic innervation.[19] Furthermore, it has been postulated that the vascular leakage seen in the iris fluorescein angiographic studies on Fuchs' heterochromic cyclitis may be caused by a disturbance in the iris vessel innervation, which is derived solely from the sympathetic nervous system.[20,21]

In a recent electron microscopic study evidence was found for a neurovascular defect involved in the pathogenesis of hemifacial atrophy.[3] The retinal vascular abnormalities seen in our patient and in those of Gass et al.[11] may result from such a neurovascular defect. These findings and the above mentioned studies point to the hypothesis of a common sympathetic defect implicated in the etiology of hemifacial atrophy and Fuchs' heterochromic cyclitis.

In addition to hemifacial atrophy, Fuchs' heterochromic cyclitis has been reported in association with other diseases; ocular toxoplasmosis[22,23], ocular trauma[24], retinitis pigmentosa[25] and the subclavian steal syndrome[26]. Moreover, recent immunohistochemical studies on iris biopsy specimens[27,28] have failed to show any specific abnormalities in these patients. It is therefore conceivable that although Fuchs' heterochromic cyclitis is a single clinical entity, it may have more than one cause.

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Chapter 7

FUCHS' HETEROCHROMIC CYCLITIS IN CONGENITAL OCULAR TOXOPLASMOSIS

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Summary- We report a follow-up after 25 years of a patient with a congenital bilateral ocular toxoplasmosis who developed Fuchs' heterochromic cyclitis in her left eye. Whether Toxoplasma gondii can cause the development of Fuchs' heterochromic cyclitis, as our case suggests, or whether the cyclitis is a secondary ocular response to a variety of different etiologic agents is not yet clear.

Introduction

Although Fuchs' heterochromic cyclitis is a distinct disease, the specific cause is still unknown. An association between Fuchs' heterochromic cyclitis and ocular toxoplasmosis is assumed because of the presence of chorioretinal scars in 7.5%-60% of patients, which are consistent with a previous intraocular toxoplasmosis.[1,2] Apart from these toxoplasmosis-like scars, nonspecific chorioretinal lesions are also described in Fuchs' heterochromic cyclitis patients.[3]

Two theories explaining the association between the fundus lesions and Fuchs' heterochromic cyclitis have been proposed. First, the fundus lesions in these patients are due to a previous Toxoplasma infection. Secondly, the scars are of non-Toxoplasma origin and may result from antibodies produced during the course of anterior segment inflammation (cross reacting with pigment bearing cells in the uvea and fundus). Until now, only sporadic cases of Fuchs' heterochromic cyclitis with an active Toxoplasma lesion or a well documented history of active ocular toxoplasmosis have been reported.[1,2] We now report, after a follow-up of 25 years, on a patient with a congenital bilateral ocular toxoplasmosis who developed unilateral Fuchs' heterochromic cyclitis.

Case Report

A four-week-old female child was seen by an ophthalmologist because of suspected congenital toxoplasmosis. Her mother had had a seroconversion in the last trimester of pregnancy (Sabin-Feldman dye test titre 1:16 384). The patient was prematurely born (gestation time: 31 4/7 weeks, weight 1790 grams). Paediatric and neurological examinations revealed no apparent abnormalities. She had a positive Sabin-Feldman dye test (titre 1:256). On ophthalmic examination the child had slight microphthalmus of the right eye (cornea diameter on the right: 8 mm, 9.5 mm on the left) and pigment on the lens. No abnormalities were seen in the fundus. At the age of 4 1/2 months the dye test titre had increased (titre 1:4096) and the patient had developed splenomegaly. An electroencephalogram, made when she was 8 months old, showed a slightly abnormal pattern which could be consistent with a diffuse encephalopathy. We diagnosed congenital toxoplasmosis based on the seroconversion in her mother in the last trimester of pregnancy, the increase of antitoxoplasmal antibodies during the first months of the patients' life, and on the clinical picture.

When the patient was 11 years old she consulted the ophthalmologist because of blurred vision in her left eye. Her visual acuity was 20/60 on the right and 20/15 on the left. In addition to the microphthalmus old atrophic hyperpigmented scars compatible with toxoplasmosis were seen in the right fundus. Examination of her left eye disclosed two active peripheral lesions of focal retinochoroiditis and a mild iritis. Both the Sabin-Feldman dye test (titre 1 :64) and the complement binding reaction (titre 1:4) were low positive. The diagnosis of active ocular toxoplasmosis was made, and the patient was treated with atropine and corticosteroids drops. Owing to the peripheral localisation of the inflammatory focus systemic therapy was considered to be not required. Within several weeks the retinal lesions sharpened and ultimately became atrophic hyperpigmented scars.

Two years later the patient returned to the ophthalmologist with complaints of floaters in her left eye (visual acuity on the right 20/60 and 20/15 on the left). Ophthalmic examination of the left eye revealed fine white keratic precipitates, scattered on the entire endothelium. Heterochromia with the left iris clearly lighter than the right iris and the absence of synechiae were noted (Fig. 1); in addition sporadic cells in the aqueous and evident vitreous opacities were observed. Fundus examination of both eyes showed old known atrophic scars; active lesions were not present (Fig. 2). Tests to exclude other causes of uveitis (serum angiotensin converting enzyme, serum lysozyme, serological tests for syphilis, Mantoux test, chest X-ray) were all within normal range. Based on the clinical picture our diagnosis was Fuchs' heterochromic cyclitis. From the age of 13 years the patient did not suffer another recurrence of ocular toxoplasmosis. Only the fluctuation in intensity of vitreous opacities, characteristic of Fuchs' heterochromic cyclitis, caused her to visit the ophthalmologist in the past 12 years.

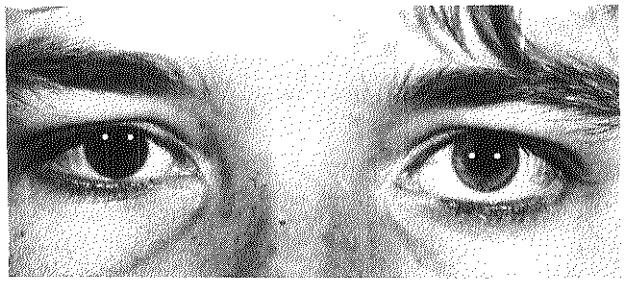

Fig. 1- Evident heterochromia in a patient with bilateral congenital ocular toxoplasmosis and Fuchs' heterochromic cyclitis of her left eye.

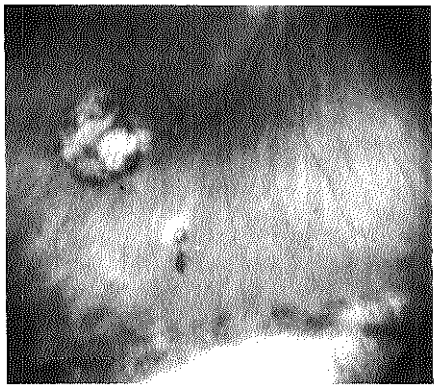

Fig. 2A- Old atrophic hyperpigmented chorioretinal scars compatible with toxoplasmosis in the right eye.

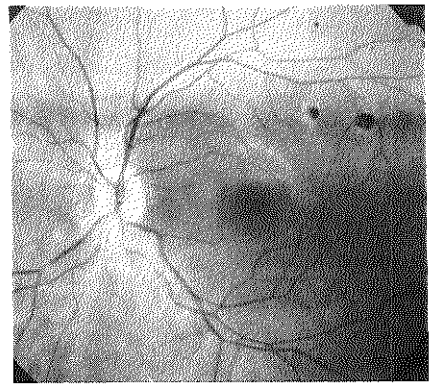

Fig 2B- Chorioretinal scars of Toxoplasma-origin in the left eye with Fuchs' heterochromic cyclitis.

Discussion

We report this case to help to elucidate the association between Fuchs' heterochromic cyclitis and ocular toxoplasmosis. During a follow-up of 25 years, starting when our patient was 4 weeks old, we recorded the appearance of active Toxoplasma lesions in the left retina when the patient was eleven years old, two years later followed by the development of a clinical picture characteristic of Fuchs' heterochromic cyclitis in the same eye. Until now only cases of presumptive ocular toxoplasmosis with clinical features of Fuchs' heterochromic cyclitis have been described. This report concerns the development of Fuchs' heterochromic cyclitis in a patient with definite congenital ocular toxoplasmosis. Our case suggests that infection with Toxoplasma gondii may cause the development of Fuchs' heterochromic cyclitis.

Whether Fuchs' heterochromic cyclitis is a secondary phenomenon that can be seen as an ocular response to a variety of different etiologic agents, is not yet clear.[4] Associations between it and other ocular diseases have been reported - retinitis pigmentosa, trauma, scars of non-Toxoplasma origin.[2,3,5] Moreover, recent immunohistochemical analysis of iris biopsy specimens in Fuchs' heterochromic cyclitis patients has failed to show any specific immunohistologic abnormality.[6] It is therefore conceivable that Fuchs' heterochromic cyclitis may be a single clinical entity with different causes.

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Chapter 8

CONTRALATERAL ACTIVE OCULAR TOXOPLASMOSIS IN FUCHS' HETEROCHROMIC CYCLITIS

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Summary- We describe a patient with unilateral Fuchs' heterochromic cyclitis who developed an active ocular toxoplasmosis in the contralateral eye, which was proved by aqueous humour analysis. Based on the current literature, including our own studies, we suggest that Fuchs' heterochromic cyclitis may be a secondary phenomenon with a spectrum of clinical features and different causes, including congenital toxoplasmosis.

Introduction

Many authors have published on the assumed association between Fuchs' heterochromic cyclitis and ocular toxoplasmosis.[1-8] Most studies reported on the presence of chorioretinal scars which were clinically consistent with a previous intraocular toxoplasmosis. In the majority of cases these toxoplasmosis-like lesions were present in the cyclitic eye. Only few patients with Fuchs' heterochromic cyclitis and active Toxoplasma retinochoroiditis have been described.[1-3,7,8] Until now, this clinical picture of toxoplasmosis was confirmed by aqueous humour analysis in two cases only.[2] In a recent study we found a significantly higher incidence of toxoplasmosis-like chorioretinal scars in patients with Fuchs' heterochromic cyclitis than in a control group of patients with a HLA-B27-positive anterior uveitis.[6] Although we found this positive clinical association between Fuchs' heterochromic cyclitis and toxoplasmosis-like scars, this association could not be substantiated by serological tests for toxoplasmosis (immunofluorescence or ELISA) or by a test for cellular immunity to Toxoplasma antigen. Analysis of aqueous humour samples for Toxoplasma antibodies also yielded negative results. One must keep in mind however, that no active chorioretinal lesions were present in the patients with Fuchs' heterochromic cyclitis at the time of blood sampling, nor at the time when the aqueous humour samples were obtained (during cataract surgery).[6]

Here, we report on a patient with unilateral Fuchs' heterochromic cyclitis who developed an active toxoplasmosis of the contralateral eye, which could be proved by aqueous humour analysis.

Case report

A 28-year old patient consulted our ophthalmology department with complaints of a diminished visual acuity of the left eye (6/6 on the right, Hand Movements; HM on the left). Ophthalmic examination disclosed small white keratic precipitates scattered on the endothelium, 1+ flare in the aqueous, diffuse iris stromal atrophy, no posterior synechiae and evident heterochromia. A dense subcapsular cataract was present. Tests to exclude other causes of uveitis were all within normal range. Based on the clinical picture our diagnosis was Fuchs' heterochromic cyclitis. The right eye showed no anterior segment abnormalities, but fundus examination disclosed small pigmented chorioretinal scars nasally. During the cataract extraction we obtained aqueous humour of the left eye after informed consent. No Toxoplasma antibodies could be detected, even in undiluted aqueous humour. The Toxoplasma antibody titre in a paired serum sample was 1:32. No fundus lesions were seen after removal of the cataract. Two years later, this patient returned with a diminished visual acuity of the right eye (6/12 on the right, 20/24 on the left). The left eye still showed the typical clinical features of Fuchs' heterochromic cyclitis, as described above. The right eye showed mutton-fat keratic precipitates, 1+ cells in the aqueous and many vitreous opacities. No iris abnormalities were seen. The fundus was difficult to examine due to many vitreous opacities; disc oedema, periphlebitis and an active focal retinochoroidal lesion could be discerned. A diagnostic anterior chamber paracentesis was performed. Using an immunofluorescence test, local intraocular antibody production against various micro-organisms was investigated, as described earlier.[9,10] A positive Goldmann-Witmer coefficient of 22 ($\geq$ 3 is considered positive[10]) was found for Toxoplasma gondii, indicating an active intraocular production of Toxoplasma antibodies.[9,10] (Table).

Table- Results of investigation of intraocular production of antibodies against various micro-organisms.

	Toxoplasma gondii	HSV	CMV	EBV	VZV
Serum titre	1 : 16	$<$1 : 16	1 : 16	1 : 256	1 : 256
Aqueous titre	1 : 4	0	0	1 : 2	1 : 4
Coefficient	22	0	0	$<$1	1.4

HSV = Herpes Simplex Virus, CMV = Cytomegalo Virus, EBV = Epstein-Barr Virus, VZV = Varicella Zoster Virus

No intraocular production of antibodies against Herpes Simplex Virus (HSV), Cytomegalo Virus (CMV), Epstein-Barr Virus (EBV) or Varicella Zoster Virus (VZV) could be detected. Based on the results of this aqueous humour analysis, a diagnosis of active ocular toxoplasmosis was made and therapy with clindamycin and sulphadiazine was started. Within several weeks the vitreous cleared; a retinochoroidal lesion typical of toxoplasmosis appeared in satellite formation next to old pigmented scars (Figure).

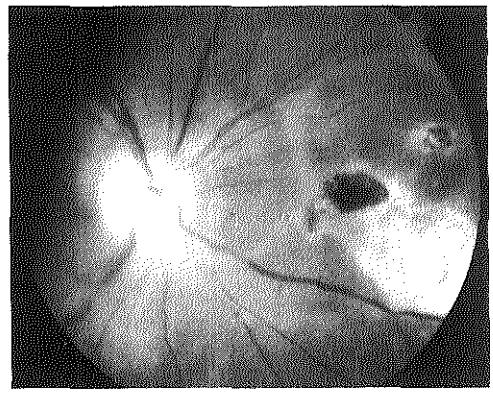

Fig.- Fundus photograph of the right eye three weeks after the therapy was started. A fresh retinochoroidal lesion typical of Toxoplasmosis appeared in satellite formation next to old pigmented scars.

Discussion

Until now, only one study reported two patients with Fuchs' heterochromic cyclitis and active Toxoplasma retinochoroiditis, in whom the clinical diagnosis of toxoplasmosis was confirmed by aqueous humour analysis.[2] We recently described a patient with a definite congenital bilateral toxoplasmosis who developed an unilateral Fuchs' heterochromic cyclitis.[4] The patient described in the current report had no clinical characteristics of toxoplasmosis in his eye with Fuchs' heterochromic cyclitis, but developed an active toxoplasmosis in the opposite eye, which could be proved by aqueous humour analysis. These few cases support the hypothesis that Fuchs' heterochromic cyclitis may be secondary to congenital toxoplasmosis.

Fuchs' heterochromic cyclitis, although considered as a separate nosological entity, has also been described in association with other (ocular) diseases; retinitis pigmentosa[11-13], ocular trauma[2,14], the subclavian steal syndrome[15], hemifacial atrophy[16] and Horner's syndrome.[17] In a recent study on the association between Fuchs' heterochromic cyclitis and toxoplasmosis several patients lacked the keratic precipitates typical of Fuchs' heterochromic cyclitis.[3] On the other hand, patients with ocular toxoplasmosis sometimes have keratic precipitates characteristic of Fuchs' heterochromic cyclitis. Occasionally also pigmented keratic precipitates are observed in patients with a typical clinical picture of Fuchs' heterochromic

cyclitis.[18] It is often difficult to make the diagnosis Fuchs' heterochromic cyclitis, since no minimal diagnostic criteria have been established internationally:[19] in fact, a spectrum of signs may be seen in patients with this disorder.[18,19] It is therefore conceivable that Fuchs' heterochromic cyclitis may be a secondary phenomenon with a spectrum of clinical features and different causes, including congenital toxoplasmosis.

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Chapter 9

IS FUCHS' HETEROCHROMIC CYCLITIS ASSOCIATED WITH OCULAR TOXOPLASMOSIS ?

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Summary- To analyze the association between Fuchs' heterochromic cyclitis and toxoplasmosis we performed ocular examinations and used various specific laboratory tests to establish a role for Toxoplasma gondii in the pathogenesis of Fuchs' heterochromic cyclitis. Results were compared with those for other types of uveitis and healthy controls. Of the 88 patients with Fuchs' heterochromic cyclitis, nine (10.2 %) had toxoplasmosis-like scars, but an association could not be proved by the indirect immunofluorescence antibody test or an Enzyme Linked Immunosorbent Assay (ELISA), or by a test for cellular immunity to Toxoplasma-antigen. Analysis of aqueous humour for Toxoplasma antibodies in patients with Fuchs' heterochromic cyclitis also yielded negative results.

Introduction

Fuchs' heterochromic cyclitis was first described in 1906 by Ernst Fuchs.[1] This low-grade chronic cyclitis, which is mostly unilateral, is characterized by small white or translucent stellate keratic precipitates scattered on the entire endothelium, a variable degree of iris (stromal-) atrophy, and the absence of synechiae. Visual deterioration may be due to vitreous opacities or subcapsular cataract formation. Cataract extractions in these patients have good results,[2,3] but secondary glaucoma, which is another complication, is not so easily controlled therapeutically.[4]

Although Fuchs' heterochromic cyclitis is considered to be a separate nosologic entity, the specific cause is still unknown. Toxoplasma gondii has been suggested as a possible etiologic agent, since in Brazil and France 60% of the patients with Fuchs' heterochromic cyclitis were reported to have chorioretinal lesions clinically consistent with toxoplasmosis.[5,6]

Arffa and Schlaegel[7] described two patients with Fuchs' heterochromic cyclitis who had fundus lesions characteristic of toxoplasmosis and negative titers for toxoplasmosis in undiluted serum. These authors also described other types of chorioretinal scars in patients with Fuchs' heterochromic cyclitis and therefore proposed that the chorioretinal scars were of non-Toxoplasma origin and resulted from autoimmunity directed against retinal or choroidal antigens.[6,7]

The aim of the present study was to analyze the association between Fuchs' heterochromic cyclitis and toxoplasmosis, by means of ocular examination and the use of various specific laboratory tests to establish this parasitic infection.

Materials and Methods

Patient selection

One hundred twelve patients with a previously made diagnosis of Fuchs' heterochromic cyclitis were requested to attend an ophthalmological examination. All 112 patients were seen at the academic eye hospital in Amsterdam or Rotterdam, the Netherlands. The previous diagnosis was confirmed by the presence of all of the following criteria, established from data in the literature:[1,2,4,8-12] (1) the absence of acute symptoms, such as severe redness, pain or photophobia; (2) the presence of characteristic small white stellate keratic precipitates; (3) minimal cells and flare in the anterior chamber; (4) diffuse iris stromal atrophy, with or without patchy loss of the iris pigment epithelium; (5) the absence of synechiae; and (6) the presence of cells and opacities in the anterior vitreous. Heterochromia, cataract and glaucoma could be present, but were not essential criteria for the diagnosis. After excluding patients for whom the diagnosis was not certain, a total of 88 patients with Fuchs' heterochromic cyclitis were included in this study (group A). Clinical data are presented in Table 1.

Fundus examination, with special attention to the peripheral retina, was also performed prospectively on a control group (B) of 98 patients with HLA-B27-positive anterior uveitis, which was not active at the moment of our examination. Examinations in group A and B were performed by two independent ophthalmologists.

Fundus lesions were categorized as characteristic of toxoplasmosis if they were one to three disc diameters in size, with a white centre and hyperpigmented borders, and flat or depressed, as described by Arffa and Schlaegel.[7] Chorioretinal lesions that were not consistent with a specific uveitis syndrome were categorized as non-specific. This included any type of abnormality of the retina or choroid or lesions compatible with antecedent or active inflammation.

Four groups of patients with uveitis (groups C through F) were selected for the various Toxoplasma laboratory tests, described below. Blood samples were obtained at the time of initial examination and stored at -20 °C, the specific laboratory tests for this study were performed later. To establish the correct diagnosis a retrospective review of clinical records

of these patients with uveitis, seen at the eye hospitals of Amsterdam and Rotterdam between 1980 and 1987, was performed. Details on mean age, age range and male to female ratio of all groups are given in Table 1.

Group C consisted of 95 patients with active ocular toxoplasmosis. This diagnosis was based on an active unilateral focal necrotizing retinochoroiditis, often in satellite formation, with associated vitreous inflammation and the appearance of typical scars with hyperpigmentation after clearing of the vitreous.[14]

Group D consisted of 20 young adults with definite congenital ocular toxoplasmosis, who were part of a prospective study based on 1821 pregnant women.[15] The diagnosis was based on the following criteria: seroconversion of the mother during pregnancy and the persistence of positive Sabin-Feldman dye test titers beyond the age of 30 months as defined in the above mentioned study.[15] No active chorioretinal lesions were present at the time of bloodsampling.

Group E consisted of 21 consecutive patients with anterior uveitis of various causes, including HLA-B27-positive anterior uveitis.

Group F included 20 consecutive patients with pan- or posterior uveitis of various causes, but not of Toxoplasma origin. A seventh group (G) consisted of 13 healthy controls.

Table 2 gives the numbers of consecutive patients and controls from all groups (A and C through F) used for the laboratory tests described in detail hereafter. For all groups blood samples were collected of consecutive patients during a specific (limited) period. Samples were therefore not available from all patients for all the different tests performed. Since samples from consecutive patients were used, no selection was made and all these patients were representative of their respective groups.

Laboratory tests

The following serological tests to establish an infection with T. gondii were performed: an indirect immunofluoresence test, as described earlier,[16] and an enzyme linked immunosorbent assay (ELISA) for detecting IgG and IgM Toxoplasma antibodies, free Toxoplasma-antigen, and circulating immune complexes containing Toxoplasma-antigen with IgG or IgM, as described previously.[17-19] The ELISA test was used in this study because earlier reports suggested that the ELISA is more sensitive than the Sabin-Feldman dye test, especially when dealing with low positive titers.[20,21] The indirect immunofluorescent antibody test has largely replaced the Sabin-Feldman dye test and is believed to be as sensitive and specific.[22] Moreover, to exclude ocular toxoplasmosis, obtaining an enzyme-linked immunoassay titre or a Sabin-Feldman titre in addition to a (negative) immunofluorescent Toxoplasma antibody titre is recommended.[22] The indirect immunofluorescence test and the ELISA tests were employed in patients with Fuchs' heterochromic cyclitis (group A) and groups C through F (Table 2).

Table 1- Clinical data of patients and controls.

Group	Diagnosis	Total number	Age, years		Sex No. (%)	
			mean ± SD	range	Male	Female
A	Fuchs' heterochromic cyclitis	88	36.7 ± 15.6	4 - 84	42 (47.7)	46 (52.3)
B	HLA-B27 positive anterior uveitis	98	43.5 ± 12.1	26 - 75	68 (69.4)	30 (30.6)
C	Active Toxoplasma uveitis	95	26.3 ± 9.4	1 - 77	54 (56.8)	41 (43.2)
D	Inactive congenital ocular toxoplasmosis	20	15.5 ± 14.0	3 - 43	10 (50.0)	10 (50.0)
E	Consecutive anterior uveitis of various etiologies	21	45.5 ± 17.1	24 - 77	12 (57.1)	9 (42.9)
F	Consecutive pan-or posterior uveitis of non-Toxoplasma origin	20	31.4 ± 11.6	11 - 65	9 (45.0)	11 (55.0)
G	Healthy controls	13	36.5 ± 6.5	29 - 52	6 (46.2)	7 (53.8)

Tests for cellular immunity (MIF-assay) to Toxoplasma-antigen were performed in patients with Fuchs' heterochromic cyclitis (group A) and groups C through G. The MIF-assay has been described in detail elsewhere.[23] The Toxoplasma-antigen used was a water-soluble extract, obtained after repeated freeze thawing and sonication of the parasite.[24]

Aqueous humour samples from patients with Fuchs' heterochromic cyclitis (group A), patients with active Toxoplasma uveitis (group C), patients with panuveitis or posterior uveitis of non-Toxoplasma origin (group F), and a separate group of patients with senile cataract were collected between 1985 and 1990 from consecutive patients, and analyzed for local intraocular Toxoplasma antibody production, as described earlier.[16] Aqueous humour was obtained during cataract surgery from consecutive patients with Fuchs' heterochromic cyclitis. A low grade uveitis was present in all patients with Fuchs' heterochromic cyclitis, but no active chorioretinal lesions were seen at the time the aqueous humour samples were obtained. Aqueous humour samples were collected during a limited period from consecutive patients, and therefore samples were not available from all patients. All patients were informed about these investigations and their consent was obtained.

The Toxoplasma antibody titre in aqueous and serum was compared with the total IgG content in aqueous and serum, and the Goldmann-Witmer coefficient was calculated, by the

following equation:

$$\frac{\text{antibody titre aqueous}}{\text{total immunoglobulin G aqueous}} : \frac{\text{antibody titre serum}}{\text{total immunoglobulin G serum}}$$

A coefficient of 3 or greater was considered positive for intraocular production of Toxoplasma antibodies.

Statistical analysis was performed by the Chi-squared test, Fisher's exact test and Kruskall-Wallis test for one way analysis of variance.

Table 2- Numbers of consecutive patients and controls used for the laboratory tests.

Group	Diagnosis	Total number	IF*	EIISA	Cellular immunity Toxoplasma antigen	Aqueous humour†
A	Fuchs' heterochromic cyclitis	62	62	52	13	30
C	Active Toxoplasma uveitis	95	95	80	35	18
D	Inactive congenital toxoplasmosis	20	20	16	0	0
E	Consecutive anterior uveitis of various causes	21	21	20	11	0
F	Consecutive panuveitis or posterior uveitis of non-Toxoplasma origin	20	20	20	10	16
G	Healthy controls	13	0	0	13	0

* IF: Indirect immunofluorescence test for detection of Toxoplasma antibodies in serum.

† Aqueous humour analysis for the detection of Toxoplasma antibodies.

Results

Fundus examination

Of the 88 patients with Fuchs' heterochromic cyclitis investigated, 20 (22.7%) had inactive chorioretinal scars. This was significantly higher ($P < .001$) than the proportion in the control group of HLA-B27 positive anterior patients with uveitis, of whom four (4.1%) out of 98 had chorioretinal scars (Table 3). Of the chorioretinal scars found in 20 patients with Fuchs' heterochromic cyclitis, nine (10.2%) resembled the scars characteristic of toxoplasmosis (toxoplasmosis-like ; Figs. 1 and 2). This was also a significantly higher incidence ($P < .005$) than in the HLA-B27 positive anterior uveitis group, in which no toxoplasmosis-like scars were found.

Table 3- Fundus examination: incidence of chorioretinal lesions

	No.(%)	
Type of chorioretinal lesion	Group A: Fuchs' heterochromic cyclitis (n=88)	Group B: HLA-B27 positive anterior uveitis (n=98)
Toxoplasmosis-like	9 (10.2)*	0 (0)
Non-specific	11 (12.5)	4 (4.1)
Total	20 (22.7)	4 (4.1)†

* $P < .005$ †$P < .001$

In 11 (12.5%) patients with Fuchs' heterochromic cyclitis chorioretinal lesions were seen that were not consistent with a specific uveitis syndrome. These lesions were usually very small (one-half disc diameter) pigmented chorioretinal scars or areas of chorioretinal atrophy of unclear origin, often located in the periphery (Figs. 3 and 4). Four (4.1%) non-specific chorioretinal lesions were seen in the control group of 98 HLA-B27-positive anterior uveitis patients.

In the 20 patients with Fuchs' heterochromic cyclitis with chorioretinal scars, 17 (85%) of the lesions were present in the eye with cyclitis and three in the normal opposite eye. Three patients had unilateral Fuchs' heterochromic cyclitis with bilateral scars. In two of these three patients, the scars were toxoplasmosis-like. Bilateral cyclitis was found in 4 (4.5%) of the 88 patients with Fuchs' heterochromic cyclitis. One of these four patients with Fuchs' heterochromic cyclitis had a toxoplasmosis-like scar in one eye; the other three patients had no chorioretinal scars.

In the HLA-B27-positive patients with anterior uveitis we observed four non-specific chorioretinal scars.

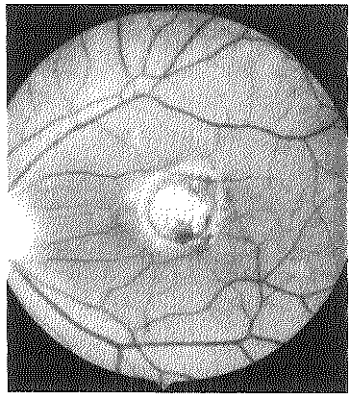

Fig. 1- Chorioretinal scar characteristic of toxoplasmosis (toxoplasmosis-like) in the left eye of a patient with ipsilateral Fuchs' heterochromic cyclitis.

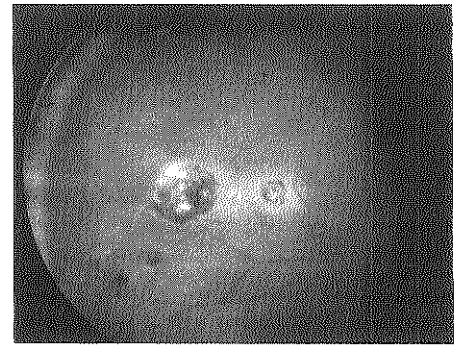

Fig. 2- Chorioretinal scars in satellite formation in the left eye of a patient with Fuchs' heterochromic cyclitis of her right eye. These toxoplasmosis-like scars were present in both eyes.

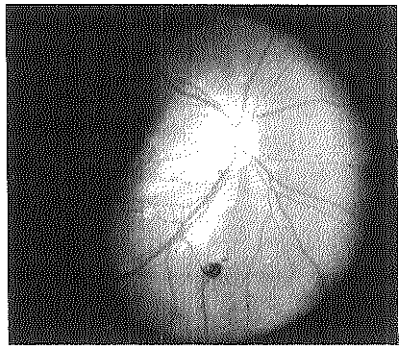

Fig. 3- Non-specific chorioretinal lesion (not consistent with a specific uveitis syndrome) in the left eye of a patient with ipsilateral Fuchs' heterochromic cyclitis, appearing as a small pigmented scar.

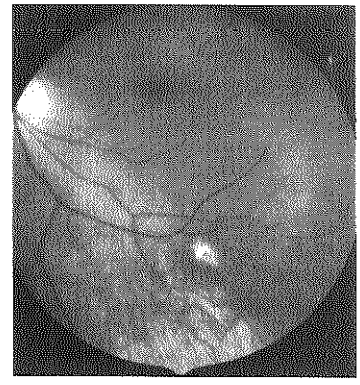

Fig. 4- Another example of a non-specific chorioretinal lesion in the right eye of a patient with ipsilateral Fuchs' heterochromic cyclitis: area of chorioretinal atrophy of unclear origin.

Toxoplasma-serologic findings

The distribution of the Toxoplasma antibody titers, measured by the immunofluorescence test, was similar in all types of uveitis investigated (groups A and groups C through F) (Kruskall-Wallis test) (Fig. 5). Within the group of Fuchs' heterochromic cyclitis, no serological differences were found between patients with toxoplasmosis-like scars, with non-specific scars, or without chorioretinal scars. All patients with Fuchs' heterochromic cyclitis with toxoplasmosis-like scars had Toxoplasma antibody titers in serum higher than 1:16. One has to keep in mind that the prevalence of antibodies against T. gondii in the normal population in the Netherlands is up to 59% in adults between 40 and 79 years.[25]

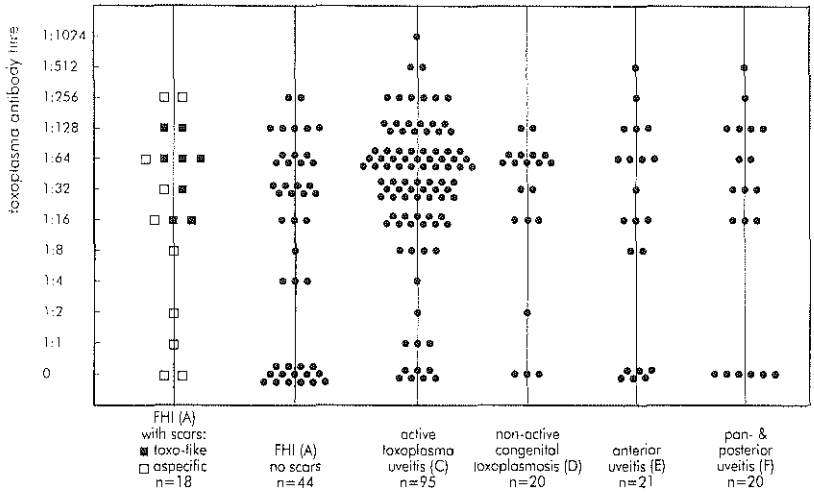

Fig. 5- Toxoplasma antibodies in serum, as determined by the indirect immunofluorescence test. A Toxoplasma antibody titre of 0 indicates no Toxoplasma antibodies in undiluted serum; 1:1, Toxoplasma antibodies present only in undiluted serum. FHI indicates Fuchs' heterochromic cyclitis; for FHI with scars, shaded squares indicate Toxoplasmosis-like lesions, and open squares, nonspecific lesions.

Titers were tested to undiluted serum, because a negative test result with undiluted serum indicates that ocular toxoplasmosis is highly improbable.[20] The number of patients without detectable Toxoplasma antibodies in undiluted serum (Fig. 5; Toxoplasma antibody titre of 0, was significantly higher in the Fuchs' heterochromic cyclitis group (patients with and without chorioretinal scars) ($P < .01$), in the anterior uveitis group ($P < .05$), or in the panuveitis / posterior uveitis group ($P < .05$) than in the group with active Toxoplasma uveitis. No significant differences were found between active Toxoplasma uveitis and congenital (inactive) ocular toxoplasmosis.

Results of the ELISA (Table 4) concerning the detection of Toxoplasma antibodies of the IgG type or an ELISA with negative findings on all measures, were significantly lower (i.e. occurred less frequently) in Fuchs' heterochromic cyclitis ($P < .001$), in consecutive anterior uveitis ($P < .05$) or in panuveitis / posterior uveitis of non-Toxoplasma origin ($P < .01$) than in active Toxoplasma uveitis. No significant differences could be demonstrated between active Toxoplasma uveitis and congenital (inactive) ocular toxoplasmosis. ELISA tests for Toxoplasma antibodies of the IgM type, circulating Toxoplasma-antigen and circulating immune complexes containing Toxoplasma-antigen with IgG or IgM yielded no significant differences between the various uveitis groups.

Of the 12 patients with Fuchs' heterochromic cyclitis with chorioretinal scars tested, three had negative results on all ELISA measures. Two of these three patients with Fuchs' heterochromic cyclitis had non-specific chorioretinal scars, and one patient had a toxoplasmosis-like scar. The Fuchs' heterochromic cyclitis patient with the toxoplasmosis-like scar and negative results of the ELISA did have a positive immunofluorescence test (titre 1:128).

Cellular immunity

Of the 13 patients with Fuchs' heterochromic cyclitis who were tested, two (15%) patients had positive cellular immune responses to the crude Toxoplasma-antigen (Fig. 6). This incidence was significantly lower ($P < .01$) than that in the group with active Toxoplasma uveitis, in which 20 (57%) out of 35 patients had positive cellular immune responses to Toxoplasma-antigen. Three of the 13 patients with Fuchs' heterochromic cyclitis tested had chorioretinal scars, two of which were consistent with toxoplasmosis. These three patients however, all had negative cellular immune responses to the Toxoplasma-antigen.

Two (18%) of the 11 patients with anterior uveitis and two (15%) of the 13 healthy controls had a positive cellular immune response to Toxoplasma-antigen. These incidence were also significantly lower ($P < .05$ and $P < .01$ respectively) than in patients with active Toxoplasma uveitis. Five (50%) out of 10 patients with panuveitis / posterior uveitis of non-Toxoplasma origin had positive responses to the crude Toxoplasma antigen, which was not significantly different from the incidence in patients with active Toxoplasma uveitis.

Aqueous humour analysis

Intraocular production of antibodies against T. gondii (Goldmann-Witmer coefficient ≥ 3), could not be demonstrated in any of the aqueous humour samples obtained from 30 patients with Fuchs' heterochromic cyclitis (Table 5). Moreover, in 28 of these 30 aqueous samples, no Toxoplasma antibodies could be detected, even in undiluted aqueous humour. One (6%) of 16 panuveitis / posterior uveitis patients and none of 30 patients with senile cataract had a positive coefficient. Of the 18 patients with active Toxoplasma uveitis, 15 (83%) had a Goldmann-Witmer coefficient of 3 or greater. Two patients with Toxoplasma uveitis had coefficients of 1.1 and 1.7, probably due to leakage of serum into the aqueous humour

(breakdown of the blood-aqueous barrier). A third patient with uveitis with a clinical diagnosis of toxoplasmosis had no detectable Toxoplasma antibodies, even in undiluted aqueous humour.

*Table 4- Toxoplasma serology with ELISA**

Group	Diagnosis	ELISA* positive No. (%)					
		IgG	IgM	CircAg	CIC/ IgG	CIC/ IgM	All ELISA measures negative No. (%)
A	Fuchs' heterochromic cyclitis (n=52)	35 (67.3)†	2 (3.8)	0 (0)	2 (3.8)	4 (7.7)	13 (25)†
C	Active Toxoplasma uveitis (n=80)	76 (95)	4 (5)	1 (1.3)	7 (8.8)	7 (8.8)	2 (2.5)
D	Congenital ocular toxoplasmosis (n=16)	14 (87.5)	2 (12.5)	0 (0)	0 (0)	0 (0)	2 (2.5)
E	Consecutive anterior uveitis (n=20)	15 (75)‡	1 (5)	0 (0)	0 (0)	0 (0)	5 (25)‡
F	Consecutive panuveitis or posterior uveitis of non-Toxoplasma origin (n=20)	13 (65)§	1 (5)	0 (0)	1 (5)	1 (5)	6 (30)§

* ELISA indicates enzyme-linked immunosorbent assay: CircAg, circulating Toxoplasma antigen; CIC/IgG circulating immune complexes containing Toxoplasma antigen with IgG; and CIC/IgM circulating immune complexes containing Toxoplasma antigen with IgM.

† $P < .001$, ‡ $P < .05$, § $P < .01$ as compared with active Toxoplasma uveitis.

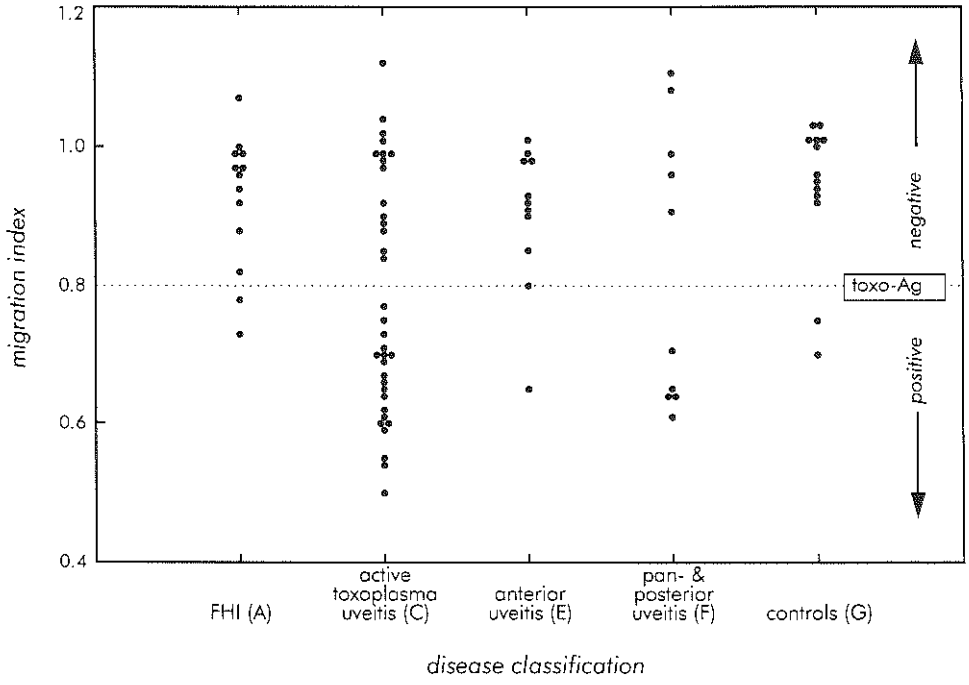

Fig. 6- Cellular immunity against the crude Toxoplasma-antigen determined by the MIF-assay. FHI indicates Fuchs' heterochromic cyclitis.

Table 5- Intraocular production of Toxoplasma antibodies (Goldmann-Witmer-coefficient ≥ 3)

Diagnosis	No.	No. with Goldmann-Witmer coefficient positive (≥ 3)
Fuchs' heterochromic cyclitis	30	0
Panuveitis or posterior uveitis of non-Toxoplasma origin	16	1
Senile cataract	30	0
Active Toxoplasma uveitis	18	15

Discussion

In this study, the incidence of chorioretinal lesions was significantly higher in patients with Fuchs' heterochromic cyclitis than in patients having HLA-B27 positive anterior uveitis. Ernst Fuchs[1] already noted chorioretinal lesions in the 38 patients with heterochromic cyclitis he described in 1906. In two of his patients, these lesions were active foci of choroiditis. He observed atrophic choroidal lesions not only in the uninvolved eye, but also in the opposite, non-involved eye. Until 1982, when de Abreu et al.[5] from Brazil reported a high incidence (56.5%) of chorioretinal lesions characteristic of toxoplasmosis in patients with Fuchs' heterochromic cyclitis, most authors did not associate these toxoplasmosis-like lesions with Fuchs' heterochromic cyclitis. In France in 1985 however, such a high incidence of toxoplasmosis-like lesions was also reported in patients with Fuchs' heterochromic cyclitis[6] (Table 6). Unfortunately, in both the studies from Brazil[5] and France[6] the incidence of toxoplasmosis-like lesions in Fuchs' heterochromic cyclitis was not compared with the incidence of these chorioretinal lesions in other types of uveitis, and no other types of retinal lesions were described. Because of the high prevalence of Toxoplasma retinochoroiditis in these countries,[26,27] the incidence of toxoplasmosis-like lesions may also be elevated in other patient groups and in the normal population.

By means of fundus examination we demonstrated a significantly higher incidence of toxoplasmosis-like lesions in patients with Fuchs' heterochromic cyclitis than in the control group of HLA-B27 positive anterior patients with uveitis from the same population. Our percentages of patients with toxoplasmosis-like lesions (10.2%), which are similar to those found by Arffa and Schlaegel[7] (7.5%) from Indiana in the United States and to a study from Italy[28] (8.4%), were much lower than those found in Brazil[5]and France.[6] Recently Schwab[29] in West-Virginia (U.S.), confirmed the earlier studies from Brazil and France; he also reported such a high incidence (64%) of toxoplasmosis-like lesions in patients with Fuchs' heterochromic cyclitis. Schwab argued that Arffa and Schlaegel[7] were very strict in their determination of scars consistent with toxoplasmosis and might have missed chorioretinal scars in the peripheral retina because they performed a retrospective review. Still, such a great difference in incidence of toxoplasmosis-like lesions in patients with Fuchs' heterochromic cyclitis between the various studies cannot be explained by these two arguments alone. Another important explanation may be that the prevalence of Toxoplasma retinochoroiditis differs between populations,[30] as evidenced by the different prevalence of antibodies against T. gondii in different populations.[25,27,31]

Although we found a positive clinical association between Fuchs' heterochromic cyclitis and toxoplasmosis-like scars, an association could not be proved by serological tests (immunofluorescence and ELISA) or by a test for cellular immunity (MIF-assay) to Toxoplasma-antigen. Serological and cellular test results of patients with Fuchs' heterochromic cyclitis were all significantly lower than those patients with active Toxoplasma uveitis and were similar to those in consecutive anterior uveitis and panuveitis or posterior patients with uveitis of non-Toxoplasma origin. One must keep in mind however, that no

active chorioretinal lesions were present in the patients with Fuchs' heterochromic cyclitis at the time of blood sampling. Moreover, Toxoplasma serology has no definite diagnostic value for ocular toxoplasmosis, since also in the general population a high prevalence of positive titers exists, mostly due to a past acquired Toxoplasma infection.

Since peripheral blood tests for Toxoplasma gondii infection in patients with Fuchs' heterochromic cyclitis yielded negative results, we analyzed aqueous humour for the presence of a local intraocular Toxoplasma antibody production. In 28 out of 30 patients with Fuchs' heterochromic cyclitis no Toxoplasma antibodies could be detected, even in undiluted aqueous humour. Our findings are in disagreement with those obtained by Saraux et al.,[6] who found an intraocular Toxoplasma antibody production in two out of three patients with Fuchs' heterochromic cyclitis with toxoplasmosis-like lesions. This discrepancy may be explained by the fact that in two of these three patients with Fuchs' heterochromic cyclitis, Saraux et al. observed an active retinal inflammation at the same time or one year before anterior chamber paracentesis. The aqueous humour samples of the 30 patients with Fuchs' heterochromic cyclitis we analyzed, were obtained during cataract surgery, and no active chorioretinal lesions were present at the time of sampling.

Table 6- Incidence of chorioretinal lesions characteristic of toxoplasmosis in patients with Fuchs' heterochromic cyclitis reported in the literature since 1982.

			Patients with chorio-	retinal lesions
Source, y	Location	No. of patients	No. (%)	Active lesions, No.
De Abreu et al.,[5] 1982	Brazil	23	13 (56.5)	2
Arffa and Schlaegel,[7] 1984	Indiana, U.S	67	5 (7.5)	0
Saraux et al.[6], 1985	France	17	11 (65)	3
Pezzi et al.[28], 1987	Italy	119	10 (8.4)	1
Schwab[29], 1991	West Virginia	25	16 (64)	3
Present study, 1991	the Netherlands	88	9 (10.2)	0

The studies from Brazil[5], France[6], Italy[28] and West-Virginia[29] reported a total of 9 patients with Fuchs' heterochromic cyclitis with active Toxoplasma retinochoroiditis. We recently described a patient with a definite bilateral congenital ocular toxoplasmosis who developed Fuchs' heterochromic cyclitis of her left eye.[32] These case reports support the hypothesis that infection with Toxoplasma gondii may lead to Fuchs' heterochromic cyclitis,

but this may concern only a very limited number of patients with Fuchs' heterochromic cyclitis. It is also possible that ocular toxoplasmosis can create a chronic condition that can resemble Fuchs' heterochromic cyclitis but not have the same pathogenesis, as suggested by Schwab.[29] The typical keratic precipitates of Fuchs' heterochromic cyclitis were absent in 5 of his 16 patients with Fuchs' heterochromic cyclitis with toxoplasmosis-like chorioretinal scars. We excluded such patients from our study because the diagnosis of Fuchs' heterochromic cyclitis was not certain in these cases. Further studies are therefore necessary to find out if patients with an original diagnosis of ocular toxoplasmosis also have the anterior segment characteristics of Fuchs' heterochromic cyclitis.

The non-specific chorioretinal scars seen in the patients with Fuchs' heterochromic cyclitis may be caused by other etiologic agent(s) or an entirely different pathologic mechanism. In our study, these non-specific scars were present in conjunction with negative laboratory results for Toxoplasma gondii. This is consistent with the suggestion of Arffa and Schlaegel[7] that such chorioretinal scars are of non-Toxoplasma origin and perhaps are the result from autoimmunity directed against retinal or choroidal antigens.

Earlier studies[33] showed that a high percentage (71%) of patients with Fuchs' heterochromic cyclitis had cellular autoimmune responses against a major soluble cornea antigen (54 KD). Furthermore, Fuchs' heterochromic cyclitis was found associated not only with ocular toxoplasmosis, but also with other ocular diseases; retinitis pigmentosa[9,33-36] and trauma[6,37]. It is therefore possible that Fuchs' heterochromic cyclitis is a secondary phenomenon: an initial infection with micro-organism(s) or another disease process may liberate potent auto-antigens, leading to a common pathway of a secondary autoimmune uveitis that becomes selfperpetuating. Perhaps the eye has only a limited clinical set of uveoretinal responses to a stimulus, whether it is immunologic, infectious or a combination of both. It is therefore conceivable that Fuchs' heterochromic cyclitis is a clinical entity in which various etiologic mechanisms are involved.

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Addendum

The major part of this study was published in the Archives of Ophthalmology (1992;110:806-811) with an altered title, as suggested by the editor. Since not all authors gave permission for this alteration, the original title of the manuscript is used in this chapter.

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Chapter 10

DOES AUTOIMMUNITY TO S-ANTIGEN PLAY A ROLE IN FUCHS' HETEROCHROMIC CYCLITIS ?

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Summary- Autoimmunity directed against retinal or choroidal antigens has been suggested to play a role in the chorioretinal lesions observed in patients with Fuchs' heterochromic cyclitis. This hypothesis was addressed and patients with Fuchs' heterochromic cyclitis were tested for cellular immunity (Migration Inhibitory Factor-assay) against human retinal S-antigen. A significantly higher percentage of patients with Fuchs' heterochromic cyclitis had a positive cellular autoimmune response to S-antigen than healthy controls or other patients with anterior uveitis. This finding is remarkable since Fuchs' heterochromic cyclitis is generally classified as an anterior uveitis and patients with Fuchs' heterochromic cyclitis without chorioretinal lesions also had a positive test. In view of these results and a sensitization against a corneal antigen reported earlier in Fuchs' heterochromic cyclitis, we suggest that a chronic low grade anterior uveitis or chorioretinitis of unknown origin may cause the release of potent auto-antigens in these patients.

Introduction

Many studies have been published to elucidate the etiology of Fuchs' heterochromic cyclitis, but it remains unknown. Although it is considered as a separate nosological entity, associations between Fuchs' heterochromic cyclitis and other diseases have frequently been described.[1-13] Most of these studies reported on the assumed association between Fuchs' heterochromic cyclitis and ocular toxoplasmosis.[1-7] In 7.5% to 60% of the patients with Fuchs' heterochromic cyclitis the presence of chorioretinal scars, which were clinically consistent with ocular toxoplasmosis was reported. In a recent study we found toxoplasmosis like chorioretinal lesions in nine (10.2%) out of 88 patients with Fuchs' heterochromic cyclitis.[7] No association between Fuchs' heterochromic cyclitis and ocular toxoplasmosis however, could be proved by extensive laboratory tests for toxoplasmosis. Furthermore,

non-specific chorioretinal scars were present in patients with Fuchs' heterochromic cyclitis along with negative laboratory results for Toxoplasma gondii. Arffa and Schlaegel[5] also observed non-specific scars in patients with Fuchs' heterochromic cyclitis. Moreover, these authors described two patients with Fuchs' heterochromic cyclitis who had fundus lesions characteristic of toxoplasmosis, but negative titers for Toxoplasma in undiluted serum. They suggested that these scars were of non-Toxoplasma origin and could result from autoimmunity against retinal or choroidal antigens.[3] We have addressed this hypothesis and looked for a possible role of retinal S-antigen in the pathogenesis of Fuchs' heterochromic cyclitis by means of a test for cellular immunity (Migration Inhibitory Factor-assay) to human S-antigen.

Patients and Methods

Patient and Control Population

Fresh blood was obtained from 13 patients with Fuchs' heterochromic cyclitis (group A) seen at the University Eye clinics in Amsterdam or Rotterdam. The diagnosis was based on the presence of all of the following criteria, established from data in the literature:[14-21](1) the absence of acute symptoms, like severe redness, pain or photophobia; (2) the presence of characteristic small white stellate keratic precipitates; (3) minimal cells and flare in the anterior chamber; (4) diffuse iris stromal atrophy, with or without patchy loss of the iris pigment epithelium; (5) the absence of synechiae; (6) the presence of cells and opacities in the anterior vitreous. Heterochromia, cataract and glaucoma could be present, but were not essential criteria for the diagnosis.

Results were compared with other types of uveitis (groups B, C and D) and healthy controls (group E). Blood samples were obtained from patients with active uveitis: some of them presented for the first time and blood samples were obtained as part of their examination for uveitis. Details on mean age, age range, male to female ratio, clinical activity of the disease and therapy at the time of testing of all groups are presented in Table 1.

Group B consisted of 39 patients with active ocular toxoplasmosis. This diagnosis was based on an active unilateral focal necrotizing retinochoroiditis, often in satellite formation, with associated vitreous inflammation and the appearance of typical scars with hyperpigmentation after clearing of the vitreous.[22] Group C consisted of 19 consecutive patients with anterior uveitis of various etiologies. Group D comprised 31 consecutive patients with pan- or posterior uveitis of various etiologies (including pars planitis n=3), that were not of Toxoplasma origin (Table 2). At the same time 26 similar blood samples were obtained from sex and age-matched healthy laboratory staff without a history of ocular pathology to serve as controls (Group E).

For all groups blood samples were collected from consecutive patients during a specific (limited) time period and no selection was made. To establish the correct diagnosis a

retrospective review of clinical records of these uveitis patients, seen at the University Eye clinics of Amsterdam and Rotterdam, was performed.

Table 1- Clinical data of patients and controls

Group	Diagnosis	Number	Male / Female	Age (years) mean	Age (years) range	Disease activity active/ low-grade	Therapy topical*	Therapy systemic†
A	Fuchs' heterochromic cyclitis	13	6 / 7	39	22 - 71	0 / 13	3	-
B	Active Toxoplasma uveitis	39	19 / 20	31	12 - 77	39 / 0	-	-
C	Anterior uveitis	19	9 / 10	49	23 - 77	19 / 0	10	-
D	Pan- and Posterior uveitis	31	15 / 16	37	11 - 72	31 / 0	11	5
E	Healthy controls	26	14 / 12	37	28 - 63	-	-	-

* steroid eye drops
† prednisone (20-40 mg/day) or prednisone (5-10 mg/day) and cyclosporin A (5-10 mg/kg/day)

Human S-antigen

Human S-antigen was isolated from retinas of human cadaver eyes from which the corneas had been removed for transplantation. These retinas were stored at -20 °C until use. The isolation of human S-antigen was performed as described by Doekes et al.[23] A 50 % ammonium sulphate precipitation of retinal extract was followed by DEAE (DE-52, Whatman Corporation, Kent, United Kingdom) anion exchange chromatography and gel filtration.[23]

Migration Inhibitory Factor (MIF) Assay

Cellular immune reactivity against human S-antigen was tested in a two-step migration inhibition assay, as described in detail earlier.[23] In the first step of this assay mononuclear cells were incubated with the test antigen. Subsequently the cell-free supernatant was tested in a second step for the presence of migration inhibitory (MIF) activity using the human monocytoid U937 cell-line as indicator cells.

Table 2- Uveitis entities included in groups C and D and their results of immune testing.

Group	Uveitis entity	Number	Positive response to S-antigen
C	Anterior uveitis	19	2
	Undetermined	12	1
	HLA-B27 associated	4*	1
	Sarcoidosis	1	-
	Syphilis	1	-
	Herpes zoster uveitis	1	-
D	Pan- and Posterior uveitis	31	12
	Undetermined	12	5†
	Sarcoidosis	4	1
	Pars planitis	3	1
	Idiopathic retinal vasculitis	2	1
	Behçet's disease	2	1
	Birdshot retinochoroidopathy	1	1
	Vogt-Koyanagi-Harada's disease	2	-
	Acute retinal necrosis	2	1
	Acute multifocal placoid pigment epitheliopathy	1	-
	Presumed ocular histoplasmosis	1	1
	Lyme borreliosis	1	-

* One patient also had ankylosing spondylitis

† One patient with diabetes mellitus developed retinal detachment and severe panuveitis after cataract extraction with intraocular lensimplantation

For the first step, mononuclear cells were isolated from heparinized blood obtained from the patients using density gradient centrifugation on Ficoll-Paque (Pharmacia, Uppsala, Sweden). Cells from one or more controls were always tested on the same day as the patient cells. The cells were washed twice and adjusted to 2.5 x 10^6 cells per ml culture medium (RPMI 1640 supplemented with 25 mM Hepes, 100 U/ml penicillin, 0.1 mg/ml streptomycin (Gibco, Ltd, Paisley, Scotland) and 10 % heat-inactivated pooled human serum from non-transfused healthy male donors (Central Laboratory of the Blood Transfusion Service, Amsterdam, The Netherlands). One ml-aliquots were dispensed into 10 ml culture tubes. One tube served as medium control for spontaneous MIF production, Concanavalin-A (Con-A; 25 μg/ml) was added to a second tube to test the general mitogenic responsiveness of the cells, and purified human S-antigen (5 μg/ml) was added to a third tube. The tubes were incubated for 20 hrs in a humified incubator at 37 °C and 5 % CO_2. Cell-free supernatants were harvested by centrifugation (10 min, 1200 g) and assayed directly for the presence of MIF or stored at -20 °C until use.

For the second step of the assay, a human monocytoid cell (U937) line was used. U937 cells were harvested from permanent in vitro cultures, washed and adjusted to 5 x 10^5 cells per ml in culture medium. Seaplaque agarose (FMC Corporation, Rockland, ME) was

dissolved in phosphate-buffered saline (20 mg/ml) at 100° C for 20 min and subsequently diluted 1:10 with warm (37 °C) culture medium. Equal volumes of the agarose solution were mixed with the U937 cell suspension and kept at 37 °C. One μl droplets were pipetted with a 50 μl Hamilton syringe into the centre of wells of a flat-bottom 96-wells microtitre tray (Nunc, Roskilde, Denmark). The droplets were allowed to set for 30 min at 4°C and subsequently 100 μl of cell-free supernatant, obtained in the first step, was added to each well. Each supernatant was tested in five-fold. The trays were incubated for 20 hr in a humified incubator at 37°C and 5 % CO_2 to allow migration of the U937 cells out of the agarose droplets. The areas of monocyte migration were measured and the migration indices (MI) were calculated as follows:

$$MI = \frac{\text{mean migration area in test supernatant}}{\text{mean migration area in control supernatant}}$$

in which the control supernatant came from the tube containing cells in culture medium alone.

A mean MI of 0.95 $\pm$ 0.07 was calculated from the values obtained from the healthy controls incubated with S-antigen. Subsequently MI values equal to or smaller than 0.8 were taken as positive reactions.

Statistical analysis was performed with the Chi-squared test and Fisher's exact test.

Results

The results are presented in the Figure. Six (46%) of the 13 patients with Fuchs' heterochromic cyclitis had a positive cellular immune response to human S-antigen. This was significantly higher ($P < .001$) than the healthy controls, who all had negative responses. Only three (8%) of the 39 patients with active Toxoplasma uveitis and two (11%) of the 19 patients with anterior uveitis had a positive cellular immune response to retinal S-antigen. In these two groups results were not statistically significant when compared with healthy controls. Twelve (39%) of the 31 pan/posterior uveitis patients had a cellular immune response to S-antigen, which was significantly higher when compared with healthy controls ($P < .001$). Table 2 presents results of the various uveitis entities included in groups C and D. Numbers were too small to detect increased responsiveness associated with a distinct uveitis entity.

To determine the specificity of the cellular immune response to S-antigen in the patients with Fuchs' heterochromic cyclitis, blood samples of these 13 patients were also tested for their cellular immune response to the 54 kD corneal antigen, as described by van der Gaag et al.[24] Seven of the 13 patients had a positive cellular immune response to this (bovine) 54 Kd antigen: three of these seven patients also showed a sensitization to S-antigen.

Discussion

Fuchs' heterochromic cyclitis is generally classified as a chronic low grade anterior uveitis. The high percentage of patients with Fuchs' heterochromic cyclitis having a positive cellular autoimmune response to retinal S-antigen, compared with other anterior uveitis patients and healthy controls, is therefore remarkable. It supports the hypothesis of Arffa and Schlaegel[3] that autoimmune reactions against retinal (S-)antigen(s) may play a role in the pathogenesis of Fuchs' heterochromic cyclitis. Of the 13 patients with Fuchs' heterochromic cyclitis we tested, two had retinal scars: one with a toxoplasmosis-like scar had a negative response and one patient with a non-specific retinal scar had a positive cellular immune response to S-antigen. These numbers were too small to conclude that there was a possible association between retinal autoimmunity and chorioretinal scars in Fuchs' heterochromic cyclitis.

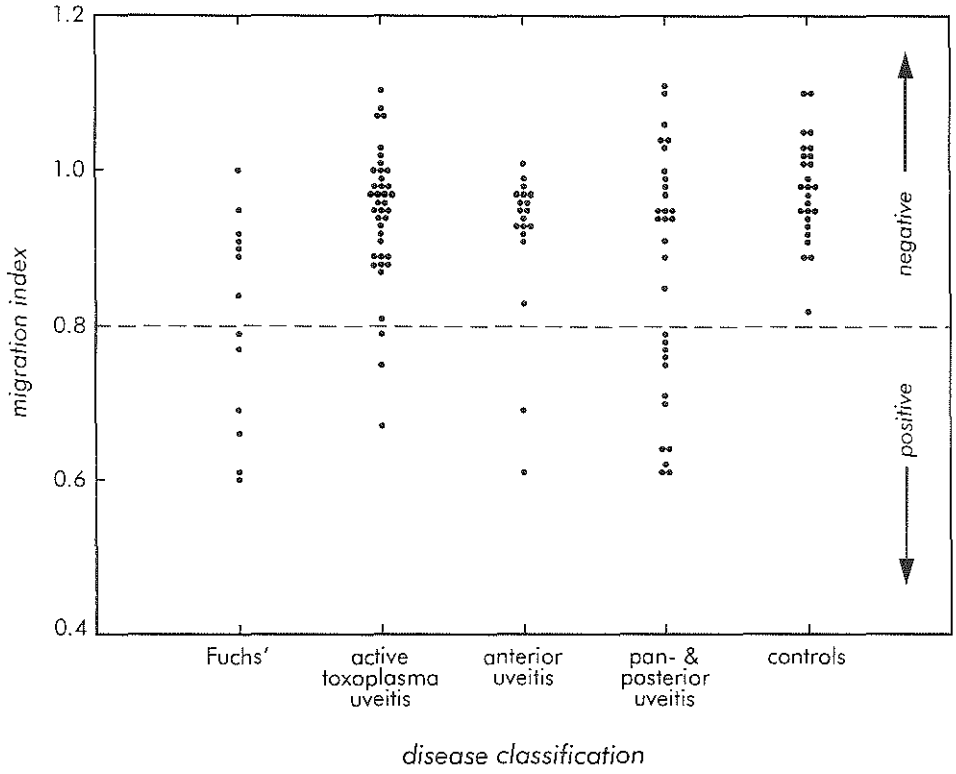

Fig.- Cellular immune reactivity against human S-antigen determined by the Migration Inhibitory Factor (MIF) Assay.

Nussenblatt et al.[25] reported a higher incidence (40 %) of cellular immune reactivity against S-antigen in patients with ocular toxoplasmosis than in our series. Such a discrepancy may be due to the fact that they[25] used a different cellular immune assay; the Lymphocyte Transformation Test (LTT). We used the MIF assay because it correlates better with type IV allergic reactions (that is delayed type hypersensitivity-(DTH)-response) than the LTT and may thus be more appropriate to study presumed autoimmune reactivity.[26]

As reported earlier,[23,27,28] a significantly higher percentage of the patients with (pan- and) posterior uveitis had a positive cellular immune response to S-antigen compared with healthy controls. These results, however, are in disagreement with more recent studies, in which no significant differences were found and normal individuals also had circulating antibodies[23,30,32] and T-cells[29-31] sensitized to retinal (S)-antigen(s). Some discrepancy may be attributed to a different procedure used to purify and obtain the S-antigen: different epitopes may have been present in the various antigen preparations. Moreover, high doses of S-antigen and extended incubation time have been shown to induce *in vitro* proliferative responses to S-antigen in T-lymphocytes of uveitis patients, but also in a large proportion of healthy donors.[31] Results of immune response testing may also vary according to the duration and activity of the disease.[29] Patients (groups B, C and D) in the current study all had active disease at the time of testing, except for the patients with Fuchs' heterochromic cyclitis (group A) who had a low-grade chronic uveitis. Whether the results may be affected by treatment is insufficiently known. Cyclosporin A (at doses 3-12 mg/kg/day) had little or no effect on the lymphocyte responses to antigens such as Keyhole Limpet Hemocyanin (KLH) or tetanus toxoid.[33] Treatment with high doses of steroids (100 and 400 mg) was reported to partially inhibit lymphocyte responses to various mitogens and antigens.[34] Except for the Toxoplasma uveitis patients, who received no therapy at the time of testing, most of the other uveitis patients in our study received either no therapy or were treated with topical steroids. Only five patients had systemic treatment: two received systemic steroids (20-40 mg/day) and three were treated with prednisone (5-10 mg/day) and cyclosporin A (5-10 mg/kg/day): 3 of these 5 patients had a positive response to S-antigen. We therefore assume that treatment only had a limited effect on the lymphocyte responses of the uveitis patients in this study.

Recently the presence of messenger RNA (mRNA) of S-antigen was demonstrated in irises obtained from uveitis patients and not in control irises.[35] These findings indicate a possible role for S-antigen in anterior segment inflammation and could account for the fact that some patients with Fuchs' heterochromic cyclitis without chorioretinal scars had a positive cellular immune response to S-antigen. This does not explain the low percentage of patients with anterior uveitis who had a positive auto-immune response to S-antigen. Fuchs' heterochromic cyclitis however, is a chronic anterior uveitis and one can imagine that there is a (more) continuous release of S-antigen than in other forms of anterior uveitis.

Earlier, it was reported that almost 70 % of all patients with Fuchs' heterochromic cyclitis had a cellular immune response against a major corneal antigen (54 kD).[24] Recently, an increased level of soluble Interleukin-2, a marker of (T)-lymphocytic activation, was

measured in the peripheral blood of patients with Fuchs' heterochromic cyclitis.[36] As in the current study, these peripheral blood findings point to a systemic lymphocytic activation, which is remarkable since it is generally believed that no systemic involvement occurs in Fuchs' heterochromic cyclitis. One could hypothesize that a primary low grade chronic anterior uveitis causes the leakage of the 54 kD in Fuchs' heterochromic cyclitis, resulting in the presence of specifically sensitized lymphocytes. Similar to the leakage of corneal antigen, a chronic low grade iritis or chorioretinitis of unknown origin may also cause the release of S-antigen, resulting in the observed sensitization. S-antigen is probably one of several antigens to which sensitization occurs, and it is therefore likely that the observed autoimmune responses in patients with Fuchs' heterochromic cyclitis may be regarded as epiphenomena.

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Chapter 11

HIGH INCIDENCE OF CORNEAL EPITHELIUM ANTIBODIES IN FUCHS' HETEROCHROMIC CYCLITIS

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Summary- Sera obtained from 26 patients with Fuchs' heterochromic cyclitis were examined for the presence of autoantibodies directed against the anterior segment of the eye by means of immunofluorescence techniques. Antibodies against human iris tissue could not be detected, whereas autoantibodies against corneal epithelium were found in almost 90% of cases. This is the first report describing the presence of circulating autoantibodies in patients with Fuchs' heterochromic cyclitis and it provides a further clue that immunological mechanisms might play an important role in the etiology of Fuchs' heterochromic cyclitis.

Introduction

Fuchs' heterochromic cyclitis is a relatively rare condition. According to Dernouchamps[1] it accounts for approximately 3% of all cases of uveitis. In 90% of the patients only one eye is affected.

The diagnosis is sometimes difficult, especially in the early stages of the disease. According to Fuchs[2] the essential features are a low grade cyclitis, including a variable degree of iris stromal atrophy, starting in the pupillary margin and causing depigmentation of the stroma. In later stages the iris pigment epithelium also becomes affected. Further clinical findings are the absence of synechiae and the presence of scattered, small, translucent keratic precipitates. Most of the patients visit the ophthalmologist with complaints of reduced vision which are caused by cataract formation or vitreous opacities.

The major causes of visual loss in heterochromic cyclitis are cataract and progressive glaucoma. Because glaucoma is a rare complication (15% of cases),[3] and cataract extraction results in the restoration of clear vision, the prognosis may be good.[4]

Various theories have been proposed to explain the etiology of Fuchs' heterochromic cyclitis. Electron microscopic studies on iris biopsies from patients with the disease reveal

a decreased number of melanocytes with relatively few, small melanin granules.[5] Earlier EM studies[6] and light microscopic studies[7] showed the presence of plasma cells and lymphocytes in the irises of these patients. The keratic precipitates, which are so typical of this disease, have been shown to represent an accumulation of lymphocytes.[8] Analysis of the aqueous humour from patients with this disease showed intraocular production of immunoglobulins; furthermore rheumatoid factor (RF) and immune complex-like material could be detected.[9] These observations strongly suggest involvement of an immunological process in the pathogenesis of the disease.

To investigate the role of the immune system in this disease we examined the incidence of autoantibodies directed against the anterior segment of the eye. No antibodies could be detected against iris or ciliary body, but surprisingly a high percentage of patients (88%) had antibodies against corneal antigens.

Materials and methods

Sera were obtained from 26 patients with Fuchs' heterochromic cyclitis (13 males and 13 females, average age 37 years) visiting the eye clinics of the universities of Amsterdam and Rotterdam. The diagnosis was made when a patient presented with a low-grade uveitis characterised by the absence of synechiae, and more or less iris (stromal) atrophy with or without heterochromia, typical keratic precipitates and often cataract. Thirty sera were also obtained from sex and age matched (healthy) persons without a history of ocular inflammation.

Sera were tested for the presence of iris, ciliary body, or cornea antibodies by an indirect immunofluorescence technique. Human irises, collected from donor eyes (from which the corneas were used for transplantation) and rabbit corneas were snap frozen in liquid nitrogen. Sections (8 μm) were cut in a cryostat, air dried on to glass slides previously coated with gelatin (1%) plus potassium-chromium (III) sulphate (0-1%) and fixed in acetone for 10 minutes. After being washed with phosphate buffered saline (PBS) the sections were incubated with a 1/10 dilution of patient or control serum in PBS for 30 minutes at room temperature. Subsequently the slides were washed three times for 10 minutes with PBS and incubated for 30 minutes in the dark at room temperature with a polyclonal, FITC conjugated goat antihuman immunoglobulin (GAHuIg-FITC, Nordic, The Netherlands) or a monoclonal, FITC conjugated mouse antihuman IgG (MoAHuIgG-FITC, CLB, The Netherlands) (both diluted 1/40 in PBS). The slides were washed thoroughly and embedded in a solution of glycerin and PBS (1:1).

Human sera containing antinuclear antibodies were used as positive controls. Tissue sections incubated with PBS instead of human sera served as negative controls.

The slides were scored in a masked fashion by two different investigators, unaware whether patient or control sera were being used, with a Leitz fluorescence microscope using the following classification: strongly positive: ++, positive: +, negative: -.

Table- Antibodies to corneal epithelium in Fuchs' heterochromic cyclitis as tested by immunofluorescence.

	Immunofluo-	rescence	score*	
	++	+	_	Percentage positive
Fuchs' heterochromic cyclitis (n=26)	18	5	3	88
Healthy controls (n=30)	1	0	29	3

* Tissue sections showing corneal epithelium antibodies after incubation with patient sera were scored by the following classification: strongly positive ++, positive +, negative -. The numbers indicate the number of patients.

Results

In the majority of patients with Fuchs' heterochromic cyclitis (88%; 23 out of 26) antibodies directed against corneal epithelium could be detected by the immunofluorescence test (IFT), whereas only one control person out of 30 had corneal antibodies (3%) (Table 1). The immunofluorescence pattern of this control person showed only cytoplasmic staining, while all the Fuchs' heterochromic cyclitis sera showed both cytoplasmic and membrane staining (Fig. 1).

Titration of the patients sera by a strong positive immunofluorescence test showed that corneal epithelium antibodies could still be detected up to a 1/40 serum dilution.

Some sera from patients with Fuchs' heterochromic cyclitis were also tested with a human cornea and a mouse cornea. These experiments showed similar results as those seen with rabbit corneas and are in agreement with earlier findings showing a large degree of cross reactivity between corneal antigens of different species.[10]

With the immunofluorescence test no antibodies could be detected in patients with Fuchs' heterochromic cyclitis (all 26 sera were tested) against normal human iris tissue. Positive control sera containing antinuclear antibodies showed a strong nuclear fluorescence staining in the iris. The detection of antibodies against human ciliary body was hindered by the fact that there was a strong background staining of endogenous immunoglobulins near the basement membrane and to a lesser degree also in the stroma (Fig. 2). This was apparent in control experiments whereby the tissue was incubated with phosphate buffered saline instead of human serum and subsequently stained with fluorescein goat antihuman immunoglobulins or a monoclonal antihuman immunoglobulin.

Discussion

Our results show a high incidence of corneal epithelium antibodies in the circulation

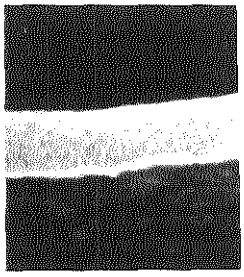

Fig. 1A- Immunofluorescence test showing antibodies in the serum of a patient with Fuchs' heterochromic cyclitis reacting with corneal epithelium.

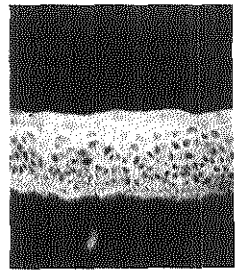

Fig. 1B: Positive serum of a healthy control.

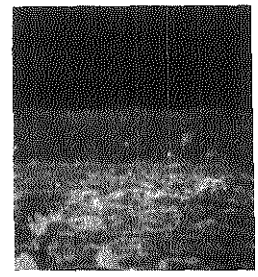

Fig.1C- Negative serum of a healthy control.

of patients with Fuchs' heterochromic cyclitis. Although the presence of circulating corneal epithelium antibodies has also been reported in other forms of uveitis, the incidence seen in patients with Fuchs' heterochromic cyclitis (88% positive) is much higher than that reported in other groups.[11,12] The incidence is 42% in anterior uveitis and 30% in posterior uveitis. The frequency of corneal epithelium antibodies in healthy controls was 3% in this study, and is similar to that reported earlier.[11] Other recent investigations[13] on the presence of serum autoantibodies (which comprised smooth muscle, nuclear material, gastric parietal cell, reticulin and mitochondria) in uveitis showed no difference between controls and patients with Fuchs' heterochromic cyclitis. Corneal epithelium antibodies are thus the first autoantibodies found in almost all patients with this disease, a finding which to our knowledge has not been reported earlier.

No antibodies could be detected against human iris. The assay for antibodies against human ciliary body was not possible because this tissue already contains large deposits of immunoglobulins near the basement membrane and stromal regions. These findings are in agreement with recent investigations[14] showing that cationic immunoglobulins traverse the fenestrated capillaries in the ciliary body and bind to anionic sites within this tissue.

The detection of autoantibodies directed against a corneal layer not involved in Fuchs' heterochromic cyclitis may appear puzzling at first sight. The corneal epithelium, however, contains a number of antigens which are shared with the corneal stroma and endothelium.[15-17] This layer is often involved in Fuchs' heterochromic cyclitis, as shown by the small keratic precipitates which have been identified as accumulations of lymphocytes. These lymphocytes may be directed against certain antigens expressed or secreted by corneal endothelial cells. Furthermore, it has been shown that the corneal epithelium shares antigens with the iris, ciliary body and lens epithelium.[10,15-18] The fact that autoantibodies directed against the cornea

mainly appear as corneal epithelium antibodies when using immunofluorescence techniques on cornea sections, is probably due to the higher density of these antigens in the corneal epithelium as compared with stroma or endothelium.

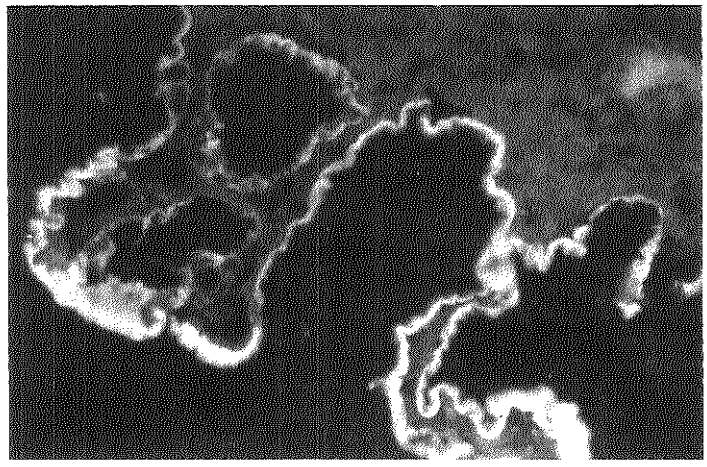

Fig. 2- Incubation of normal human ciliary body with phosphate buffered saline followed by staining with fluorescein labelled goat antihuman immunoglobulins. Note strong staining of the basement membrane.

It is not yet clear whether the corneal autoimmunity which was apparent in various forms of uveitis and especially in Fuchs' heterochromic cyclitis, is directed against the same antigen(s) or whether each entity has its own characteristic antigen. Furthermore, it has not been clarified yet if the autoimmune reactions against corneal antigens have a primary role, implicating Fuchs' heterochromic cyclitis as an autoimmune disease, or if these immunological reactions are a secondary phenomenon due to permeability changes in the anterior segment of the eye. The increased permeability of vessels in patients with Fuchs' heterochromic cyclitis can lead to a greater accessibility of corneal antigens to the immune system, which may result in an autoimmune response against these antigens. A possible important role of the immune system in Fuchs' heterochromic cyclitis is already apparent from the original description of plasma cells in the irises of these patients by Fuchs himself.[2] The accumulation of inflammatory cells on the endothelial side of the cornea is also in agreement with this hypothesis. Further evidence comes from studies by Dernouchamps,[19] who revealed the intraocular production of immunoglobulins in these patients. Whether the locally produced antibodies are directed against corneal antigens remains to be investigated. Rheumatoid factor and immune-complex-like material have also been observed in the aqueous humour of these patients.[9] The findings mentioned above in combination with our detection of corneal autoimmunity in such a high percentage of patients support the hypothesis that immunological mechanisms may play an important part in Fuchs' heterochromic cyclitis.

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Chapter 12

IMMUNE DEPOSITS IN IRIS BIOPSIES FROM PATIENTS WITH FUCHS' HETEROCHROMIC CYCLITIS

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Summary- To investigate whether Fuchs' heterochromic cyclitis 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 cyclitis, twelve patients with various 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 cyclitis. Immunoglobulin G, IgA, IgM and complement were detected in patients with Fuchs' heterochromic cyclitis 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.

Introduction

Fuchs' heterochromic cyclitis is a distinct clinical entity of still 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 cyclitis is complicated by glaucoma in 15-20% of cases.[1-4]

A vascular pathogenesis involving the iris vessels is one of the hypotheses for the etiology of Fuchs' heterochromic cyclitis.[5] The characteristic filiform haemorrhage 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 ischaemia, frequently associated with neovascularisation.[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] It was postulated that this narrowing of the vessel lumen, ultimately leading to occlusion, may be the result of immune complex deposition, and that Fuchs' heterochromic cyclitis may be an immune complex vasculitis.[5,11]

Immune complexes have been detected in the aqueous humour and serum of patients with Fuchs' heterochromic cyclitis.[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]

Until now, no evidence has been provided concerning the hypothesis of an immune complex vasculitis of the iris vessels in Fuchs' heterochromic cyclitis patients. 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 cyclitis. Results were compared with those of patients without uveitis and of patients with other types of uveitis.

Materials and Methods

Iris biopsy specimens (from peripheral iridectomies) were obtained from nine patients with Fuchs' heterochromic cyclitis (mean age ± SD: 39.1 ± 15.9, range: 25 to 77 years, four women and five men), and twelve patients with various other types of uveitis (mean age ± SD: 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 cyclitis were being treated systemically, but two were using topical corticosteroid preparations and one was using topical antiglaucoma medication. Of the 12 patients with other types of uveitis two were being treated with systemic non-steroid anti-inflammatory drugs, seven were being treated with topical corticosteroid preparations, and three patients were being treated with topical antiglaucoma preparations at the time of the operation.

Iris specimens were also obtained from nine patients without uveitis (mean age ± SD: 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 topical antiglaucoma medication at the time of the operation. We chose glaucoma patients as controls, rather than patients undergoing extracapsular cataract extraction for senile 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. Cryostat sections of 4-μm thickness were fixed in acetone for ten minutes and subsequently air-dried and rinsed in phosphate-buffered saline, pH 7.4. Slides were then incubated for one hour at room temperature with a panel of polyclonal rabbit antibodies in phosphate-buffered saline containing 0.02% gelatin and 0.1% sodium azide. The following antibodies were used: anti-human IgG, IgA and IgM, all labelled with FITC (De Beer medicals, Hilvarenbeek, the Netherlands), used in a direct (one-step) method, and anti-human complement (C3c + C3d + C4), fibrinogen, C1q and C3 (CLB, 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 the slides, after rinsing them in phosphate-buffered saline, were incubated for half an our at room temperature with FITC-labelled polyclonal horse anti-rabbit immunoglobulins (CLB). Subsequently all slides were rinsed in phosphate-buffered saline.

One slide from each specimen was stained with haematoxylin and eosin to evaluate the following pathologic features typical for Fuchs' heterochromic cyclitis: (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 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 in a masked fashion by two independent observers (E.L.H. and C.M.M.), unaware of the diagnosis, with a Leitz fluorescence microscope using a 25 x magnification. 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 is summarized in the Table. No extra-cellular immune deposits were observed outside the vessel walls. The findings in patients with Fuchs' heterochromic cyclitis 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 ($P = .001$) were found in a significantly higher number of irises obtained from patients with Fuchs' heterochromic cyclitis 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

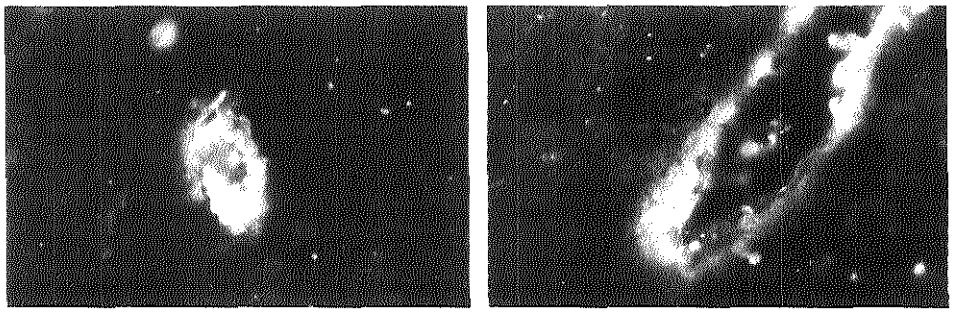

Fig. 1- Iridectomy specimen from a patient with Fuchs' heterochromic cyclitis. Left, Granular IgM deposits in vessel wall (× 630). Right, Granular IgA deposits in vessel wall (× 630).

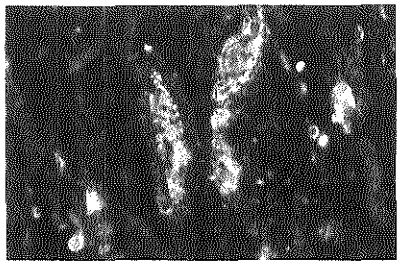

Fig. 2- Iridectomy specimen from a patient with idiopathic recurrent anterior uveitis. Granular fibrinogen deposits in vessel walls (× 400).

Fig. 3- Iridectomy specimen from a patient with Fuchs' heterochromic cyclitis 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 (haematoxylin and eosin, × 250).

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 out of nine irises obtained from patients with Fuchs' heterochromic cyclitis and in six of the twelve irises from patients with uveitis. IgG, IgA, and IgM were found 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 topical corticosteroids and the presence or absence of specific immune deposits. However, in the two patients with uveitis who were treated with systemic non-steroid anti-inflammatory drugs, no immune deposits were found.

Pathologic features typical of Fuchs' heterochromic cyclitis (Fig. 3) were observed with haematoxylin and eosin staining in eight of the nine irises obtained from patients with Fuchs' heterochromic cyclitis patients. No characteristics of vasculitis were observed by lightmicroscopy 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 cyclitis 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.

Table- Immune deposits in iris vessel walls of patients with Fuchs' heterochromic cyclitis, patients with uveitis, and patients with glaucoma

Immune deposits	No. (%) of patients with immune deposits, Fuchs, n=9	Difference*	No. (%) of patients with immune deposits, uveitis, n=12	Difference†	No. (%) of patients with immune deposits, glaucoma, n=9
IgG	4 (44)	P=.041	1 (8)	P=.571	0
IgA	4 (44)	P=.041	4 (33)	P=.083	0
IgM	7 (78)	P=.007	6 (50)	P=.072	1 (11)
Complement	7 (78)	P=.001	5 (42)	P=.039	0
C1q	2 (22)	P=.235	3 (25)	P=.165	0
C3	4 (44)	P=.041	4 (33)	P=.083	0
Fibrinogen	4 (44)	P=.041	6 (50)	P=.017	0

* Fuchs' compared with glaucoma patients

† Uveitis compared with glaucoma patients

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 cyclitis. However, no specific immunofluorescence staining pattern could be identified in the irises of patients with Fuchs' heterochromic cyclitis. The immune deposits observed in patients with Fuchs' heterochromic cyclitis 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 from the deposition of circulating immune complexes in the iris vessel walls.

Earlier studies demonstrated circulating immune complexes in the serum and aqueous humour of patients with Fuchs' heterochromic cyclitis.[11,12] Circulating immune complexes occur in many auto-immune diseases. Recently detected cellular and humoral immunity directed against corneal antigens suggest a role of autoimmune reactions in the pathogenesis of Fuchs' heterochromic cyclitis.[24,25] However, patients with Fuchs' heterochromic cyclitis 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 (SLE), ocular manifestations are uncommon,[26] and to our knowledge, the clinical findings typical for Fuchs' heterochromic cyclitis have never been reported in such patients. 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 cyclitis, these complexes 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 et al. on cultured human umbilical vein endothelial cells.[27]

Recent investigations of systemic vasculitis focused on the presence of anti-endothelial cell autoantibodies. Sera from patients with systemic lupus erythematosus contained both complement-fixing antibodies and immune complexes that could bind to cultured human

umbilical vein endothelial cells.[28] Anti-endothelial 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 anti-endothelial cell antibodies lyse cultured vascular endothelial cells only when these cells have been exposed previously to gamma interferon, interleukin-1 or tumour necrosis factor. These inflammatory mediators probably induce certain target antigen(s) 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 humour of patients with Fuchs' heterochromic cyclitis.[34] Therefore, it would be interesting to investigate whether anti-endothelial cell antibodies are present in the serum and aqueous humour of patients with Fuchs' heterochromic cyclitis.

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 on Fuchs' heterochromic cyclitis clearly demonstrated leakage from the iris vessels,[7,8] we found no light-microscopic evidence of a vasculitic process in this study. The hyalinization of iris vessel walls we found in all our patients with Fuchs' heterochromic cyclitis or uveitis was also seen to some degree in the irises of patients with glaucoma and may not be an abnormal finding.[21] Immunoglobulin deposition in vessel walls is known to occur in several auto-immune disorders, but it is not clear what these deposits mean in the absence of an inflammatory vascular process by light microscopy. 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 Schonlein 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]

In summary, no specific immune deposits could be identified in the irises of patients with Fuchs' heterochromic cyclitis 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 cyclitis as compared with the findings in other uveitis entities.[21] Therefore, although Fuchs' heterochromic cyclitis may be a single clinical entity, it may not be caused by one specific (immuno-) pathogenic mechanism.

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Chapter 13

FURTHER CONSIDERATIONS ON THE ETIOLOGY AND PATHOGENESIS OF FUCHS' HETEROCHROMIC CYCLITIS: CURRENT AND PREVIOUS STUDIES

Many hypotheses about the etiology of Fuchs' heterochromic cyclitis have been proposed since Ernst Fuchs first described this disease in 1906. Chapter 2 contains a summary of these theories, and a number of them have been investigated in this thesis. In this last chapter, I have tried to highlight the most important findings on the etiology of Fuchs' heterochromic cyclitis in my thesis, and coupled them with previous reports which contained valuable clues for the pathogenesis of Fuchs' heterochromic cyclitis. On this basis, I have formulated a number of highly speculative remarks, which include ideas for further research. As the reader can conclude from my "notes", there is probably not one solution for the etiology of this eye disease. Rather, Fuchs' heterochromic cyclitis seems a complex disease with various clinical features and multiple causes.

The high incidence of cellular immunity (reported by van der Gaag et al.[1]) and humoral immunity (this thesis)[2] against corneal antigens in patients with Fuchs' heterochromic cyclitis, may be associated with the typical keratic precipitates. It is tempting to speculate that the diffuse scattering of these keratic precipitates on the corneal endothelium in Fuchs' heterochromic cyclitis represents (cellular) immune responses to (a) corneal antigen(s), in comparison with the usually inferior distribution of keratic precipitates in other forms of anterior uveitis.[1,2] Indeed, as reported by Foets,[3,4] human corneal endothelial cells should be considered as "active" immunomodulating cells
because of their ability to express MHC class II antigens and immune adhesion molecules. The sensitization against retinal S-antigen found in patients with Fuchs' heterochromic cyclitis (this thesis)[5], is even more conspicuous. The recent demonstration of m-RNA for S-antigen in irides of uveitis patients and not in control irides,[6] may indicate a possible role for S-antigen in anterior segment inflammation. Furthermore, it may give an explanation for the fact that also patients with Fuchs' heterochromic cyclitis without chorioretinal lesions had a positive cellular autoimmune response to S-antigen. Arrocker[7] and Murray[8] independently demonstrated that a high proportion of patients with Fuchs' heterochromic cyclitis had an increased level of interleukin-2 receptor (IL-2R), which is a marker of (T-)lymphocytic activation. Such a high incidence of cellular autoimmunity against various ocular antigens is remarkable.

One has to keep in mind that the eye is an immunologic privileged site, as evidenced by the ACAID (Anterior Chamber Associated Immune Deviation) phenomenon: when soluble antigens are placed within the anterior chamber, a systemic antigen-specific inhibition of Delayed Type Hypersensitivity (DTH) to this antigen occurs.[9,10] Also within the anterior chamber itself, expression of cell-mediated immunity of the Delayed Type Hypersensitivity (DTH) is strongly inhibited.[11,12] The aqueous humour in normal eyes seems to be a powerful inhibitor of certain aspects of antigen-driven T-cell function, a capacity which may be largely conferred by the cytokine Transforming Growth Factor-β (TGF-β) secreted by iris and ciliary body parenchymal cells, and the neuropeptides α-Melanocyte Stimulating Hormone (α-MSH) and Vasoactive Intestinal Peptide (VIP) produced by ocular neurons.[13-20] As demonstrated by Streilein et al., intracameral injections of a subinflammatory dose of Interferon-γ (IFN-γ), a cytokine that antagonizes TGF-β, resulted in a disturbance of this immunosuppressive microenviroment and the development of severe intraocular inflammation.[21]

In Fuchs' heterochromic cyclitis, this immunosuppressive mechanism (ACAID), may be diminished; the increased lymphocytic sensitization found in these patients points in this direction. Perhaps the concentration of the immunosuppressive TGF-β is decreased as a result of the atrophic process of the iris, also affecting the parenchymal cells. However, Fuchs' heterochromic cyclitis is a mild inflammation, and other, perhaps specific anti-inflammatory intraocular factors in this disease may lead to the restoration of a (new) balanced situation, in contrast with other types of uveitis, in which a more pronounced inflammation occurs.

The highly increased permeability of the blood-aqueous barrier in Fuchs' heterochromic cyclitis, first described by Amsler and Verrey,[22] is a remarkable finding. It permits the leakage of many inflammatory mediators into the anterior segment of the eye. Yet, Fuchs' heterochromic cyclitis is always a low-grade inflammation. This also suggests the presence of some sort of equilibrium in this eye disease, perhaps maintained by unknown anti-inflammatory factor(s).

Dernouchamps et al.[23] demonstrated the presence of immune-complex-like material in the aqueous humour of nine (81 %) out of 11 patients with Fuchs' heterochromic cyclitis. They suggested a pathogenic role for immune complexes in this eye disease, since these "immune complexes" were found in a much lower percentage (5/13 = 38 %) in other types of uveitis. Their findings however, still need to be confirmed with standard techniques, because these authors used an unusual (i.e. not commonly accepted) immune complex assay.

Deposits of immunoglobulins and complement, an indirect proof for the presence of immune complexes, were found in the vessel walls of the iris from patients with Fuchs' heterochromic cyclitis and not in control irides (this thesis)[24]. However, no light-microscopic evidence for an inflammatory vascular process could be detected. Further studies are therefore necessary to determine the pathogenic role of these "immune deposits" and to find out whether they result from local formation or originate from the circulation. Moreover, it would be interesting to investigate the expression of (inflammatory) adhesion molecules on the iris vessel walls in patients with Fuchs' heterochromic cyclitis. For instance, ICAM-1,

an adhesion molecule, which plays a central role in mediating cell-cell adhesion during inflammation, may be expressed on activated vascular endothelium and thereby promote the influx of (sensitized) specific lymphocytes.[25] The presence of adhesion molecules in irides, and especially on the endothelium of the iris vessels in patients with Fuchs' heterochromic cyclitis is subject of further investigation.

The above mentioned "immune deposits" were however, also found in patients with other types of uveitis, and no specific pattern was found in Fuchs' heterochromic cyclitis (this thesis)[24]. Also in earlier studies with modern sensitive techniques, no specific (immuno-) histopathologic abnormalities could be detected in the irides of patients with Fuchs' heterochromic cyclitis.[26]

The detection of oligoclonal IgG bands in the aqueous humour of patients with Fuchs' heterochromic cyclitis and not in patients with other types of uveitis by Murray et al.[27], seems to be the only specific (immunologic) abnormality detected in these patients until now. It may imply that a small number of intraocular B-cells is stimulated by an (as yet unidentified) specific antigen, which may be part of an infectious agent or an intraocular auto-antigen. This B-cell stimulation may be the result of interleukin-6 (IL-6) production, demonstrated in the aqueous humour of patients with Fuchs' heterochromic cyclitis by the same authors. Recently, it was demonstrated by others, that the cytokine IL-6, which does not influence adhesion molecule expression on other cells, significantly unregulated ICAM-1 expression on melanocytes.[28]

Skin melanocytes have recently been shown to be capable of processing and presenting antigenic peptide fragments (after stimulation with IFN-γ) to cytotoxic T-cell clones in an MHC-II restricted manner (Le Poole, thesis)[29,30]. Such melanocytes may thus function as target cells in T-cell mediated (auto-)immune reactions, leading to the destruction of these melanocytes with areas of depigmentation of the skin, as may be seen in vitiligo, a presumed autoimmune disease (Le Poole, thesis).[30] Whether autoimmune reactions against melanocytes play a role in Fuchs' heterochromic cyclitis has not yet been investigated.

In vitiligo, perilesional melanocytes have been shown to behave morphologically and biochemically as nerve cells: they become increasingly dendritic and may even synthesize adrenalin, a neurotransmitter of the sympathetic nerve system.[31,32] This finding may be of interest when considering the sympathetic theory for Fuchs' heterochromic cyclitis. Evidence accumulates that iris hypopigmentation may be caused by a defective production of melanin due to inadequate function of adrenergic nerves.[33-43] For instance, the iris hypopigmentation in patients with Horner's syndrome may be caused by a defective sympathetic innervation, on condition that it exists for many years.[33,34] In Fuchs' heterochromic cyclitis, still other factors or conditions that cause the (mild) inflammatory signs may play a role. In addition to the iris hypopigmentation caused by a sympathetic defect, a defect in the adrenergic innervation[44] of the blood vessels of the iris, may cause the increased permeability of the blood-aqueous barrier[45-47] with subsequent leakage of proteins, cells and inflammatory

mediators into the aqueous. On can hypothesize that neuropeptides released by the sympathetic nerve system, may influence the function of the vascular endothelial cells.

Such a (local) adrenergic defect may be congenital (that is, acquired during pregnancy) or it may be secondary to an inflammatory or autoimmune process of the iris. No autoantibodies against iris tissue could however, be demonstrated in patients with Fuchs' heterochromic cyclitis (this thesis)[2]. Also in other types of uveitis some iris atrophy occurs, probably secondary to the inflammatory process. In Fuchs' heterochromic cyclitis, the process of atrophy and depigmentation is much more pronounced, and it appears to be the most discriminatory feature when histopathological findings in iris tissue from patients with Fuchs' heterochromic cyclitis are compared with those in other types of uveitis. It seems likely that a long-standing sympathetic defect may play a pathogenic role in Fuchs' heterochromic cyclitis. Because the stromal melanocytes of the iris are derived from the neural crest, it is important to remark that TGF-β has been suggested to play a crucial role in the differentiation of neural crest cells into the connective tissues of the eye during embryogenesis.[48] Furthermore, it has been demonstrated that TGF-β causes regression of blood vessels. [48] It would therefore be interesting to investigate the neural innervation and expression of neuropeptides in irides and aqueous humour of patients with Fuchs' heterochromic cyclitis, using modern immunohistochemical techniques.

Clinically, Fuchs' heterochromic cyclitis is considered to be a separate nosological entity. Often it has, however, been described in association with other diseases, of which toxoplasmosis is well known.[49-57] A causal relationship between Fuchs' heterochromic cyclitis and active ocular toxoplasmosis is difficult to establish on the basis of a few case reports. An association between Fuchs' heterochromic cyclitis and "toxoplasmosis-like" scars suggestive of an in utero acquired Toxoplasma infection, was proved in a larger study in which a control group was included (this thesis and previous reports).[54] This clinical association could however, not be substantiated by extensive laboratory tests (this thesis), which may be due to the absence of active chorioretinal lesions in the patients with Fuchs' heterochromic cyclitis at the time of blood or aqueous sampling, and the high incidence of anti-toxoplasma titers in the general population.[54]

Moreover, if an epidemiological association between Fuchs' heterochromic cyclitis and toxoplasmosis exists, one would expect a higher prevalence of patients with both diseases in the general population than calculated by multiplying the frequency of the separate eye diseases in a general population. The figures of Vadot et al.[58], in their study on the prevalence of uveitis in a normal population in the Savoy, may be used for such a calculation: 1.8/100.000 (prevalence Fuchs' heterochromic cyclitis) x 3.9/100.000 (prevalence ocular toxoplasmosis) = 0.00007/100.000 (7×10^{-9}) for the coïncidence of both eye diseases. This figure remains to be investigated.

One can only speculate how in some patients, a congenital Toxoplasma gondii infection may lead to the clinical picture typical of Fuchs' heterochromic cyclitis. Toxoplasmal cysts have been found in the iris. Furthermore, Nussenblatt[59] suggested that the inflammatory

retinal response in ocular toxoplasmosis is, at least in part, autoimmune. Also in Fuchs' heterochromic cyclitis a secondary autoimmune response may play a role. When a mother is infected during pregnancy, the neurotrophic Toxoplasma parasites may migrate into the retina. In utero, in patients with Fuchs' heterochromic cyclitis, the Toxoplasma parasites may have also migrated into the iris. By causing a local destruction of these tissues (iris, retina), a release of potent ocular antigens into the circulation may result, leading to a sensitization against retinal (S)-antigen(s) and/or iris antigens. A cellular autoimmune response to S-antigen could be demonstrated in patients with Fuchs' heterochromic cyclitis (this thesis)[5]. Whether a cellular immune response against iris antigens exists in patients with Fuchs' heterochromic cyclitis has not been investigated. One can also imagine that, if the Toxoplasma parasites have gained access to the iris during pregnancy, they may have altered the production of TGF-β and the neuropeptides α-MSH and VIP, by a local destruction of the iris and ocular neurons. This may lead to a disturbance of the immunosuppressive properties of the aqueous humour (ACAID) and subsequently the development of an anterior uveitis. Indeed, recently TGF-β was found to be decreased in experimental uveitis.[60] Thus, it seems that, via a complex pathway of a secondary (auto)immune response, a congenital Toxoplasma gondii infection may be responsible for the secondary development of Fuchs' heterochromic cyclitis in a small subset of patients.

In addition to toxoplasmosis, Fuchs' heterochromic cyclitis has been reported in combination with a retinitis pigmentosa-like clinical picture[61-63], ocular trauma[49,64], the subclavian steal syndrome[65], hemifacial atrophy[66-70], Horner's syndrome[33,71,72] and Moebius syndrome[73]. Whether Fuchs' heterochromic cyclitis occurs more often in these diseases than other types of uveitis has not been investigated. It may be that because Fuchs' heterochromic cyclitis is such a conspicuous clinical entity, it is noticed more often. In a recent study on the association between Fuchs' heterochromic cyclitis and toxoplasmosis several patients lacked the characteristic keratic precipitates.[49] On the other hand, patients with ocular toxoplasmosis sometimes have keratic precipitates resembling the typical keratic precipitates of Fuchs' heterochromic cyclitis (Figs 1 and 2). Occasionally, also pigmented keratic precipitates or posterior synechiae have been observed in patients with a typical clinical picture of Fuchs' heterochromic cyclitis. In fact, a spectrum of signs may be seen in patients with this disorder. Alternatively, it may also be difficult to make the diagnosis Fuchs' heterochromic cyclitis, since often not all characteristic features are present at the same time.

The term Fuchs' heterochromic cyclitis is merely descriptive; there is (still) no diagnostic test for this eye disease. Moreover, it is hardly likely that the clinical "syndrome" of Fuchs' heterochromic cyclitis has a single etiology.[74] Many pathogenic mechanisms have been proposed, which all made sense in some aspects. Fuchs' heterochromic cyclitis may have multiple causes. A number of different abnormalities may trigger the eye, which may have only a limited set of uveoretinal responses, to react in a particular (path)way, yielding the clinical end-state of Fuchs' heterochromic cyclitis. Such a stimulus may be immunologic, infectious or a combination of both. It may cause the release of potent autoantigens, leading

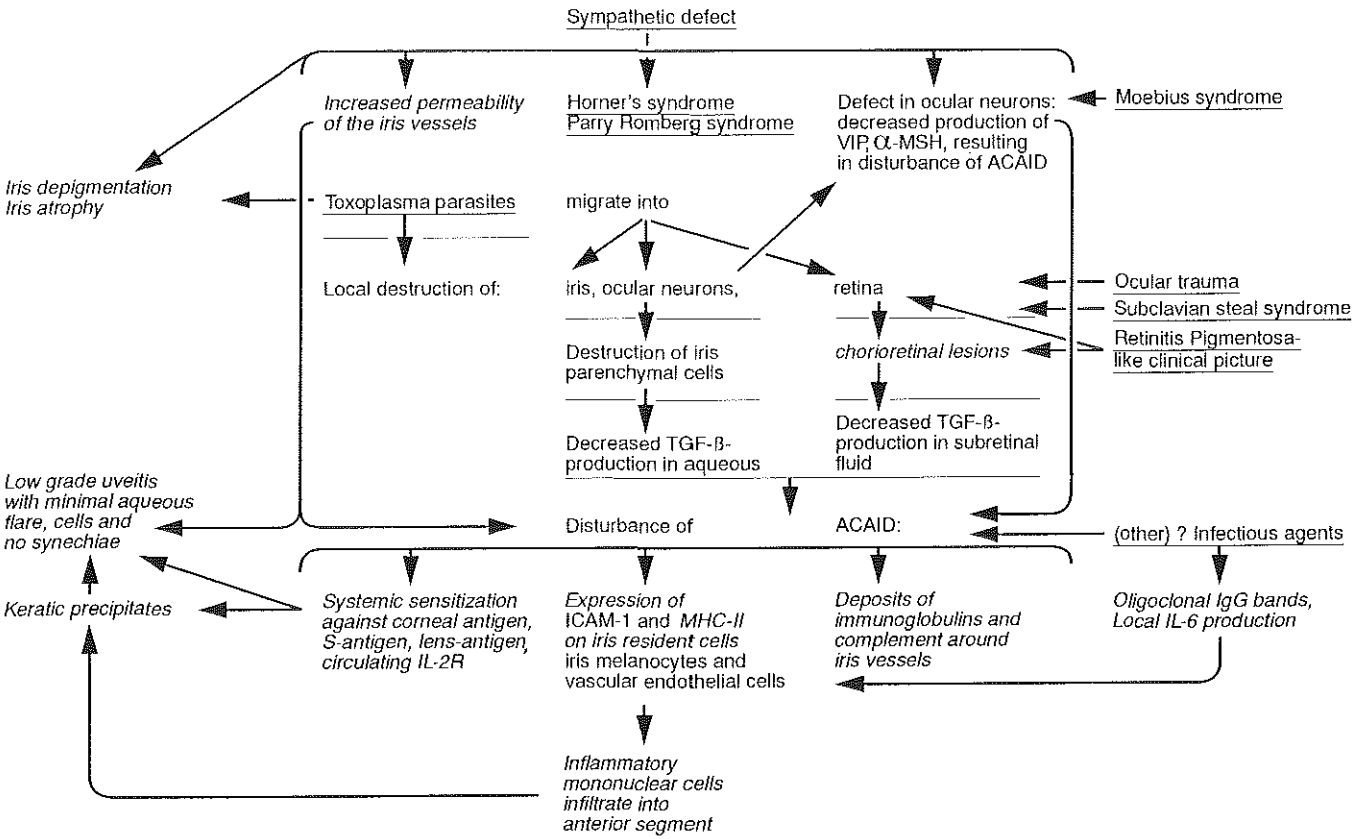
to a common pathway of a secondary autoimmune uveitis that becomes self-perpetuating. Fuchs' heterochromic cyclitis is therefore probably a secondary phenomenon with a spectrum of clinical features and multiple causes (including congenital toxoplasmosis).(Fig. 1)

Fig 1- (see next page) Schematic diagram of Fuchs' heterochromic cyclitis as secondary phenomenon. Underlined are the causes which may lead to Fuchs' heterochromic cyclitis. Clinical and (immuno-) histopathological findings in this eye disease have been printed in italic. All other findings and etiopathogenic mechanisms in this diagram are hypothetical.

Fuchs' heterochromic cyclitis

Pathogenesis

"Associated diseases"



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Chapter 14

SUMMARY

Fuchs' heterochromic cyclitis is a low-grade, chronic non-granulomatous anterior uveitis of still unknown origin, which occurs in approximately 5 % of all patients with uveitis. Cataract and glaucoma are two major complications of this eye disease. A subcapsular cataract develops in almost all cases, whereas glaucoma occurs in approximately 20 % of the cases. It was the aim of this thesis to study the clinical aspects and etiology of Fuchs' heterochromic cyclitis.

Chapter 1 is a general introduction to Fuchs' heterochromic cyclitis and presents the aim of this thesis. Chapter 2 is an up to date review of the literature on Fuchs' heterochromic cyclitis. Various clinical features and the complications (cataract and glaucoma) are described, and the therapy is discussed. Although many patients with Fuchs' heterochromic cyclitis are treated with topical steroids, which may give a slight improvement of visual acuity, the disease is never cured by such treatment. Cataract extractions with or without lens implantation currently have excellent results. Medical therapy for secondary glaucoma is still unsuccessful. Filtration surgery seems to have a more favourable outcome (see also chapter 4 of this thesis) than reported in earlier studies, due to the use of fibrosis-inhibitors. In histopathologic studies on iris tissue from patients with this disease, depigmentation, inflammatory signs and atrophy were found. These abnormalities were however, not specific for Fuchs' heterochromic cyclitis. Many hypotheses for the etiology of Fuchs' heterochromic cyclitis have been proposed since Fuchs first presented his theory for this disease in 1906. All these theories on etiological mechanisms in Fuchs' heterochromic cyclitis (Sympathetic Theory, Hereditary Theory, Association with Toxoplasmosis, Vascular Theory and Immunologic Theory) and their current value, are summarized in chapter 2.

Chapter 3 presents the results of a clinical analysis of 51 patients with Fuchs' heterochromic cyclitis. None of the patients had acute signs or symptoms (severe redness, pain or photophobia). Characteristic keratic precipitates (88 %) and/or minimal aqueous cells and flare (60 %) and vitreous opacities (84 %) were major signs, indicating a chronic inflammatory activity, in which no synechiae (100 %) were present. Heterochromia (82 %) was not a constant sign, but iris stromal atrophy was always present (100 %). Cataract was encountered in 82 % as a result of the chronic cyclitis. Secondary glaucoma was found in 22 % of the patients. Based on the predominant clinical findings obtained from this analysis and on data in the literature, we proposed clinical diagnostic criteria for Fuchs' heterochromic cyclitis. It is still necessary to determine the validity of these diagnostic

criteria by analyzing also other types of uveitis, which are difficult to differentiate from Fuchs' heterochromic cyclitis.

Chapter 4 describes the evaluation of the therapy and prognosis of secondary glaucoma in patients with Fuchs' heterochromic cyclitis, after a review of records of 111 patients with this disease. Results are based on 30 (27 %) of these 111 patients who had glaucoma or could be considered as "glaucoma suspects". Maximal medical therapy was unsuccessful in 73 % of the cases. Surgical intervention (mostly trabeculectomies, half with 5-fluorouracil) successfully controlled intraocular pressure ($\leq$ 21 mm Hg with or without medication) in 13 (72 %) of the 18 operated patients after a mean follow-up of 26 months. All successfully operated patients retained a visual acuity of 20/80 or better. We had favourable results, possibly because of modern surgical techniques (use of 5-fluorouracil, sodium hyaluronate) and earlier surgical intervention.

Chapter 5 presents the first *in vivo* study that quantifies the translucency caused by iris depigmentation in Fuchs' heterochromic cyclitis. Intraocular stray light was measured by the "direct compensation technique", and translucency of the iris and the surrounding ocular wall was quantified with a modification of this technique in both eyes of patients with Fuchs' heterochromic cyclitis. Intraocular stray light proved to be significantly higher in all patients with Fuchs' heterochromic cyclitis (both eyes) than in normal controls. Translucency of the iris was increased, even in patients without heterochromia or with a minimal degree of iris atrophy. Moreover, it was found that the process of atrophy and depigmentation in patients with Fuchs' heterochromic cyclitis is probably not restricted to the iris, but also occurs in the surrounding ocular wall. Further studies, including other uveitis groups, are necessary to investigate whether this technique can be used as a diagnostic method in Fuchs' heterochromic cyclitis.

In chapter 6, a case of progressive hemifacial atrophy (Parry-Romberg-syndrome) with a combination of ipsilateral Fuchs' heterochromic cyclitis and retinal vascular abnormalities is described. This case is interesting since recently evidence was found for a neurovascular defect in hemifacial atrophy. Our case not only supports the (clinical) association between Fuchs' heterochromic cyclitis and hemifacial atrophy, but the retinal vascular abnormalities found in this patient add further support to the existence of such a neurovascular defect. These findings and our short review of the literature point to the hypothesis of a common sympathetic defect, implicated in the etiology of both Fuchs' heterochromic cyclitis and progressive hemifacial atrophy.

In chapter 7, a patient with a definite congenital bilateral ocular toxoplasmosis, who later developed a Fuchs' heterochromic cyclitis in her left eye, is reported after a follow-up of 25 years. This case supports the hypothesis that Toxoplasma gondii can cause the development of Fuchs' heterochromic cyclitis.

Chapter 8 describes a patient who had no clinical characteristics of toxoplasmosis in his eye with Fuchs' heterochromic cyclitis, but later developed an active toxoplasmosis in the opposite eye, which could be proved by aqueous humour analysis. Assuming that the

occurrence of these two diseases is not a coincidence, this case suggests that a (subclinical) congenital Toxoplasma infection may cause the secondary development of Fuchs' heterochromic cyclitis.

In chapter 9, the association between Fuchs' heterochromic cyclitis and toxoplasmosis is analyzed by performing ocular examinations and various specific laboratory tests to establish a role for Toxoplasma gondii in the pathogenesis of Fuchs' heterochromic cyclitis. A significantly higher incidence (10 %) of toxoplasmosis-like chorioretinal scars was found in 88 patients with Fuchs' heterochromic cyclitis than in a control group of 98 patients with an HLA-B27-positive anterior uveitis (0 %). Although this positive clinical association between Fuchs' heterochromic cyclitis and toxoplasmosis-like scars was found, it could not be substantiated by serological tests for toxoplasmosis (immunofluorescence and ELISA) nor by a test for cellular immunity to Toxoplasma antigen. Analysis of aqueous humour samples for Toxoplasma antibodies also yielded negative results. One must keep in mind however, that no active chorioretinal lesions were present in the patients with Fuchs' heterochromic cyclitis at the time of blood sampling, nor at the time that the aqueous humour samples were obtained (during cataract surgery). Moreover, Toxoplasma serology has no definite diagnostic value for ocular toxoplasmosis, since also in the general population a high prevalence of positive titers exists, mostly due to a past acquired Toxoplasma infection.

In chapter 10, the hypothesis whether autoimmunity directed against retinal or choroidal antigens plays a role in the pathogenesis of chorioretinal lesions in Fuchs' heterochromic cyclitis is evaluated, by testing patients with Fuchs' heterochromic cyclitis, patients with other types of uveitis and healthy controls for cellular immunity (Migration Inhibitory Factor-assay) against human retinal S-antigen. A significantly higher percentage of patients with Fuchs' heterochromic cyclitis had a positive cellular autoimmune response to S-antigen than healthy controls or other patients with anterior uveitis. This finding is remarkable since Fuchs' heterochromic cyclitis is generally classified as an anterior uveitis and patients with Fuchs' heterochromic cyclitis without chorioretinal lesions also had a positive test. S-antigen is probably one of several antigens to which sensitization occurs, since an immune response against a corneal antigen and lens antigens have also been reported in Fuchs' heterochromic cyclitis. It was suggested that a chronic low grade anterior uveitis or chorioretinitis of unknown origin may cause the release of potent auto-antigens in these patients. It is not clear whether these autoimmune responses may be regarded as an epiphenomenon or whether they are really pathological.

In chapter 11, the hypothesis whether humoral autoimmunity directed against the anterior segment of the eye plays a role in the pathogenesis of Fuchs' heterochromic cyclitis is evaluated, by means of an immunofluorescence technique. Antibodies against human iris tissue could not be detected, whereas autoantibodies against corneal epithelium were found in almost 90% of the 26 patients. The corneal epithelium contains a large number of antigens which are also found in the corneal stroma and endothelium. It is therefore tempting to

speculate that these autoantibodies may be related to the keratic precipitates observed in Fuchs' heterochromic cyclitis.

In chapter 12, the hypothesis whether Fuchs' heterochromic cyclitis may be an immune complex vasculitis is assessed by means of an immunofluorescence technique to detect immunoglobulins and complement in iris biopsy specimens from nine patients with Fuchs' heterochromic cyclitis, twelve patients with various other types of uveitis, and nine patients with glaucoma but without uveitis. No specific immune deposits were found in the irides of the patients with Fuchs' heterochromic cyclitis. Immunoglobulin G, IgA, IgM and complement were detected in patients with Fuchs' heterochromic cyclitis and patients with uveitis, and these results differed significantly from the group without uveitis. The immune deposits were found only in the iris vessel walls. 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. No light-microscopic evidence of an inflammatory vascular process could however, be detected. It would be interesting to investigate whether the immune reactants originate from the circulation or result from local formation.

Chapter 13 contains considerations on the etiology and pathogenesis of Fuchs' heterochromic cyclitis on the basis of studies presented in this thesis and earlier reports by other authors. The most important findings for the pathogenesis of this mostly unilateral, low-grade, chronic eye disease are: the increased vascular permeability of the iris vessels, the systemic sensitization against various ocular antigens, the association with congenital toxoplasmosis and possible other diseases, and a possible defect of the sympathetic nerve system which may be responsible for the iris hypopigmentation. The only currently acceptable explanation for this eye disease may therefore be that Fuchs' heterochromic cyclitis probably is a clinical end-state (that is a secondary phenomenon) triggered by various stimuli (infectious, immunologic) and has multiple causes. A schematic diagram for this hypothesis is added to chapter 13.

SAMENVATTING

De heterochrome cyclitis van Fuchs is een milde, chronische niet-granulomateuze anterieure uveitis met nog steeds onbekende oorzaak, die voorkomt in ongeveer 5 % van de totale uveitis populatie. Cataract en glaucoom zijn twee belangrijke complicaties die optreden bij dit ziektebeeld: een achterste schors cataract ontstaat uiteindelijk in bijna alle patiënten, terwijl glaucoom zich ontwikkelt in ongeveer 20 % van de gevallen. Het doel van dit proefschrift was om de klinische aspecten en etiologie van de heterochrome cyclitis van Fuchs te bestuderen.

Hoofdstuk 1 is een algemene introductie tot de heterochrome cyclitis van Fuchs. Tevens komt in dit hoofdstuk het doel van deze dissertatie aan de orde. Hoofdstuk 2 is een overzicht van de literatuur over de heterochrome cyclitis van Fuchs. De verschillende klinische verschijnselen worden beschreven en de therapie wordt bediscussieerd. Hoewel patiënten met de heterochrome cyclitis van Fuchs vaak worden behandeld met locale corticosteroiden, die een (geringe) verbetering van de visus kunnen geven, kan deze oogziekte nooit worden genezen door deze behandeling. Cataract extracties met of zonder lensimplantatie geven tegenwoordig goede resultaten. De medicamenteuze therapie voor secundair glaucoom heeft meestal weinig succes. Filtratie chirurgie heeft een gunstiger resultaat (zie ook hoofdstuk 4) dan in eerdere studies werd gerapporteerd, met name door het gebruik van fibrose remmers. In histopathologische studies op iris weefsel van patiënten met de heterochrome cyclitis van Fuchs werden depigmentatie, ontstekingsverschijnselen en atrofie aangetroffen. Deze afwijkingen zijn echter niet specifiek. Sinds Fuchs zijn theorie over de etiologie van deze oogziekte presenteerde in 1906, zijn er verscheidene andere theorieën naar voren gebracht. Al deze theorieën over de etiologische mechanismen van de heterochrome cyclitis van Fuchs (Sympathische Theorie, Erfelijkheids Theorie, Associatie met Toxoplasmose, Vasculaire Theorie en Imunologische theorie) en hun huidige perspectieven worden besproken in hoofdstuk 2.

In hoofdstuk 3 worden de resultaten van een klinische analyse van 51 patiënten met de heterochrome cyclitis van Fuchs gepresenteerd. Bij geen van de patiënten werden acute verschijnselen (ernstige roodheid, pijn of fotofobie) gevonden. Karakteristieke descemet stippen (88 %) en / of geringe voorste oogkamer prikkeling (60 %) en glasvocht troebelingen (84 %) waren belangrijke verschijnselen, duidend op een chronische ontsteking, waarbij echter nooit synechiae posteriores werden gevonden. Heterochromie was niet altijd aanwezig (82 %), maar iris stroma atrofie werd in 100 % van de gevallen waargenomen. Secundair glaucoom werd gevonden in 22 % van de patiënten. Op basis van de meest voorkomende klinische verschijnselen uit deze analyse, en op basis van gegevens uit de literatuur, hebben wij klinische criteria voor de diagnose heterochrome cyclitis van Fuchs opgesteld. Het is wel noodzakelijk nog de waarde van deze diagnostische criteria te bepalen door middel van klinische analyse van ook andere vormen van uveitis, die moeilijk zijn te differentieren van de heterochrome cyclitis van Fuchs.

Hoofdstuk 4 beschrijft de evaluatie van de therapie en prognose van secundair glaucoom bij patiënten met de heterochrome cyclitis van Fuchs, na een retrospectieve analyse van 111 patiënten met deze oogziekte. Resultaten zijn gebaseerd op 30 (27 %) van deze 111 patiënten die glaucoom hadden of konden worden beschouwd als "glaucoma suspects". Maximale medicamenteuze therapie faalde in 73 % van de gevallen. Chirurgische interventie (voornamelijk trabeculectomieën, waarvan de helft met 5-fluorouracil) leverde een succesvolle controle op van de oogdruk ($\leq$ 21 mm Hg) in 13 (72 %) van de 18 geopereerde patiënten na een gemiddelde follow-up van 26 maanden. Alle succesvol geopereerde patiënten behielden een visus van 20/80 of beter. Onze chirurgische resultaten lijken gunstiger dan eerdere studies, wat mogelijk toegeschreven kan worden aan het gebruik van modernere chirurgische technieken (gebruik van 5-fluorouracil, Healon) en eerdere chirurgische interventie.

Hoofdstuk 5 presenteert de eerste *in vivo* studie die de translucentie ten gevolge van iris depigmentatie in deze patiënten kwantificeert. Intraoculair strooilicht werd gemeten met behulp van de "directe compensatie techniek", en de translucentie van de iris en de oogwand rond de iris werd gemeten met een modificatie van deze techniek in beide ogen van patiënten met de heterochrome cyclitis van Fuchs. Intraoculair strooilicht was significant verhoogd in patiënten met de heterochrome cyclitis van Fuchs (beide ogen) ten opzichte van normale controles. De translucentie van de iris was verhoogd, ook in patiënten zonder heterochromie of met een minimale iris stroma atrofie. Bovendien werd gevonden dat het proces van atrofie en depigmentatie in deze patiënten zich waarschijnlijk niet beperkt tot de iris, maar ook optreedt in de oogwand rond de iris. Verdere studies met andere uveitis groepen zijn nodig om te bepalen of deze techniek diagnostische waarde heeft voor de heterochrome cyclitis van Fuchs.

In hoofdstuk 6 wordt een patient met een progressieve hemifaciale atrofie (Parry-Romberg syndroom) beschreven met een combinatie van ipsilaterale heterochrome cyclitis van Fuchs en vaatafwijkingen in de retina. Deze patient is interessant omdat recent bewijs is gevonden voor een neurovasculair defect in hemifaciale atrofie. Onze patient ondersteunt niet alleen de (klinische) associatie tussen de heterochrome cyclitis van Fuchs en het Parry-Romberg syndroom, maar de vaatafwijkingen in de retina bij deze patiënt leveren nog eens extra bewijs voor het bestaan van zo'n neurovasculair defect. Deze bevindingen en een kort overzicht van de literatuur wijzen in de richting van een gemeenschappelijk sympathisch defect, dat een rol zou spelen in de etiologie van de heterochrome cyclitis van Fuchs en het Parry-Romberg syndroom.

In hoofdstuk 7 wordt een patiënte met een definitieve bilaterale congenitale oculaire toxoplasma infectie, die een de heterochrome cyclitis van Fuchs in haar linker oog ontwikkelt, gepresenteerd, na een follow-up van 25 jaar. Deze patient ondersteunt de hypothese dat Toxoplasma gondii het ontstaan van de heterochrome cyclitis van Fuchs kan veroorzaken.

Hoofdstuk 8 beschrijft een patient zonder verschijnselen van toxoplasmose in zijn oog met de heterochrome cyclitis van Fuchs, die later een actieve toxoplasma infectie van zijn contralaterale oog ontwikkelt, die middels voorste oogkamer water analyse bewezen kon worden. Als men aanneemt dat het samen optreden van deze ziekten niet op toeval berust, suggereert deze patient dat een (subklinische) congenitale Toxoplasma infectie de secundaire ontwikkeling van de heterochrome cyclitis van Fuchs kan veroorzaken.

In hoofdstuk 9 wordt de associatie tussen de heterochrome cyclitis van Fuchs en toxoplasmose geanalyseerd door middel van fundus onderzoek en verschillende specifieke laboratorium testen (immunofluorescentie, ELISA), om een mogelijke rol van Toxoplasma gondii in de pathogenese van de heterochrome cyclitis van Fuchs vast te stellen. Er werd een significant hogere incidentie (10 %) van toxoplasma-achtige chorioretinale littekens in 88 patiënten met de heterochrome cyclitis van Fuchs gevonden dan in een controle groep van 98 patiënten met HLA-B27 geassocieerde anterieure uveitis (0 %). Alhoewel deze positieve klinische associatie werd gevonden, kon hiervoor geen bewijs worden geleverd door middel van serologische testen voor toxoplasmose of met behulp van een test voor de cellulaire immuniteit tegen het Toxoplasma antigeen. Ook analyse van voorste oogkamer water op toxoplasma antistoffen leverde een negatief resultaat op. Men moet echter bedenken, dat er geen actieve chorioretinale laesies aanwezig waren in onze patiënten met de heterochrome cyclitis van Fuchs op het moment dat we bloed of voorste oogkamer water (tijdens cataract extracties) afnamen. Bovendien heeft Toxoplasma serologie geen definitieve diagnostische waarde voor oculaire toxoplasmose omdat ook in de algemene bevolking een hoge prevalentie van positieve titers aanwezig is, die voornamelijk het gevolg is van een in het verleden doorgemaakte Toxoplasma infectie.

In hoofdstuk 10 wordt de hypothese geëvalueerd of autoimuniteit tegen retinale of choroidale antigenen een rol speelt in de pathogenese van de chorioretinale laesies in de heterochrome cyclitis van Fuchs, door patiënten met de heterochrome cyclitis van Fuchs, patiënten met andere vormen van uveitis en gezonde controles te testen op hun cellulaire immuun respons (Migration Inhibitory Factor Assay) tegen humaan retinaal S-antigeen. Een significant hoger percentage patiënten met de heterochrome cyclitis van Fuchs had een cellulaire autoimmuun respons tegen S-antigeen dan normale controles of andere patiënten met anterieure uveitis. Dit is een opvalllende bevinding omdat de heterochrome cyclitis van Fuchs meestal wordt geclassificeerd als een anterieure uveitis, en ook patiënten zonder chorioretinale laesies een positieve test hadden. S-antigeen is waarschijnlijk één van de antigenen waartegen een cellulaire immuunrespons onstaat, daar al eerder over een cellulaire autoimmuun respons tegen een cornea antigeen bij patiënten met de heterochrome cyclitis van Fuchs werd gerapporteerd. Waarschijnlijk veroorzaakt een chronische milde anterieure uveitis of chorioretinitis van onbekende oorzaak in deze patiënten het vrijkomen van potentiele autoantigenen. Het is niet duidelijk of deze autoimmuun responsen beschouwd moeten worden als een epifenomeen of dat ze echt pathologisch zijn.

In hoofdstuk 11 wordt de hypothese geëvalueerd of humorale autoimmuniteit tegen het voorsegment van het oog een rol speelt in de pathogenese van de heterochrome cyclitis van Fuchs door middel van een immunofluorescentie techniek. Antistoffen tegen humaan iris weefsel konden niet worden aangetoond, maar antistoffen tegen cornea epitheel werden in bijna 90 % van de patiënten gevonden. Het epitheel van de cornea bevat een groot aantal antigenen die men ook kan aantreffen in het stroma en endotheel. Het is daarom ook goed mogelijk dat deze autoimmuun respons tegen cornea-epitheel te maken heeft met de descemet stippen in de heterochrome cyclitis van Fuchs.

In hoofdstuk 12 wordt de hypothese onderzocht of de heterochrome cyclitis van Fuchs een immuuncomplex vasculitis is, door middel van een immunofluorescentie techniek voor de detectie van immunoglobulinen en complement in irisbiopsieen van 9 patiënten met de heterochrome cyclitis van Fuchs, 12 patiënten met verschillende andere vormen van uveitis, en 9 patiënten met glaucoom zonder uveitis. Er werden geen specifieke immuundeposities gevonden in de irissen van patiënten met de heterochrome cyclitis van Fuchs. Immunoglobuline G, IgA, IgM en complement werden aangetroffen in patiënten met de heterochrome cyclitis van Fuchs en uveitis, en deze resultaten waren significant verschillend van de groep zonder uveitis. De immuundeposities werden alleen gevonden in de irisvaatwanden. Alhoewel het enige bewijs voor de aanwezigheid van immuuncomplexen de detectie van het betreffende antigeen is, suggereert de depositie van zowel immunoglobulines als complement de aanwezigheid van immuuncomplexen in de vaatwanden van de iris. Er werd echter geen licht-microscopisch bewijs voor een inflammatoir ontstekings proces van de iris vaatwanden gevonden. Het zou interessant zijn om te onderzoeken of de immuundeposities uit de circulatie komen of lokaal zijn gevormd.

Hoofdstuk 13 beschrijft overwegingen betreffende de etiologie en pathogenese van de heterochrome cyclitis van Fuchs gebaseerd op studies uit deze dissertatie en eerdere studies van andere auteurs. De belangrijkste bevindingen wat betreft de pathogenese van deze unilaterale, milde, chronische oogontsteking zijn: de verhoogde vaatpermeabiliteit van de iris vaten, de verhoogde cellulaire autoimmuniteit tegen verschillende oog-antigenen, de associatie met congenitale toxoplasmose en mogelijk ook met andere ziekten, en een mogelijk defect van sympathische zenuwen die de iris hypopigmentatie bij deze patiënten veroorzaakt. De enige op dit moment plausibele verklaring voor deze oogziekte is daarom dat de heterochrome cyclitis van Fuchs waarschijnlijk een klinisch eindstadium (secundair phenomeen) is, uitgelokt door verschillende stimuli (infectieuze en immunologische) en meerdere oorzaken heeft. Een schema voor deze hypothese is toegevoegd aan hoofdstuk 13.

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CURRICULUM VITAE

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