Causes and frequency of blindness in patients with intraocular inflammatory disease

Aniki Rothova, Maria S A Suttorp-van Schulten, W Frits Treffers, Aize Kijlstra

Abstract

Aims/Background—Uveitis, an intraocular inflammatory disease, is a significant cause of visual impairment. It is not known how many patients with uveitis will retain visual acuity and how many develop visual impairment or even blindness. The aim of this study was to assess the frequency of blindness in patients with uveitis and, more specifically, to identify the clinical profile of patients at risk for visual loss.

Methods—A cross sectional and retrospective study of 582 patients with uveitis who visited the ophthalmology departments of two university hospitals in the Netherlands was performed.

Results—Within the group of 582 patients, 203 (35%) exhibited blindness or visual impairment; bilateral legal blindness developed in 22 (4%) patients, 26 (4.5%) had one blind eye with visual impairment of the other, and nine (1.5%) had bilateral visual impairment. Unilateral blindness developed in 82 (14%) patients, whereas 64 (11%) exhibited unilateral visual impairment. The most important cause of both blindness and visual impairment was cystoid macular oedema (29% and 41%, respectively). Complications of uveitis were encountered in more than half of the patients and 23% underwent one or more surgical procedures. When the patients were subdivided according to anatomical site, those with panuveitis had the worst visual prognosis. The systemic diseases associated with a poor visual prognosis were juvenile chronic arthritis and sarcoidosis. Ocular toxoplasmosis was the most frequent cause of unilateral visual loss.

Conclusions—Cystoid macular oedema is the most frequent complication of uveitis and its occurrence plays a decisive role in the visual outcome of this disease.

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Uveitis, an intraocular inflammatory disease, is a major cause of severe visual impairment. The number of patients blind as a result of uveitis is unknown; it has been estimated that uveitis accounts for 10% to 15% of all cases of total blindness in the United States.1 The decrease in visual acuity may be attributable to cataract formation, secondary glaucoma, vitreous opacities, cystoid macular oedema, retinal scars, and other causes.2 The prevalence of uveitis reported in 1984 was 38 per 100 000 in a general population: the annual incidence was approximately 17 per 100 000 with maximum incidence in the 25 to 44 year age group.3 In surveys of the causes of blindness uveitis is usually not included and is probably underestimated. The sequelae of uveitis are considered to be the direct cause of visual loss (for example, cataract, glaucoma) while the primary cause of the decrease in visual acuity (uveitis) is not mentioned. In a recent hospital based survey of blindness in West Africa, in which these sequelae were correctly attributed to uveitis, this disease was the second leading cause of blindness; this indicates how large the proportion of patients with uveitis is among the blind.4 In the Netherlands (1975–7), in a hospital based study, uveitis caused 6% of all blindness and ranked fifth after diabetic retinopathy, age-related macular degeneration, tapetoretinal dystrophy, and glaucoma.5 In the 1993 annual report of Research to Prevent Blindness, an estimated 2 300 000 Americans suffer visual impairment because of this major sight robbing disease.6

It is not known how many patients with uveitis retain useful visual acuity and how many develop a visual handicap or even blindness. We therefore performed a retrospective study of 582 patients with uveitis of various origins to assess the frequency of blindness and visual handicap in that population and, more specifically, to identify the clinical profile of uveitis patients at risk for visual impairment.

Subjects and methods

The study included 280 consecutive patients with uveitis who visited the ophthalmology department of the University Hospital in Utrecht during 1993 and were followed for more than 1 year and 302 patients with uveitis followed for more than 1 year and chosen at random (numeric code) from the data bank of patients from the Academic Medical Centre in Amsterdam. Both institutions combine secondary and tertiary ophthalmological care; patients are referred by ophthalmologists from a large area and also by general practitioners from a smaller local area. When the patients from the two study locations were compared, their general characteristics such as male to female ratio, unilateral or bilateral involvement, site of the inflammation, tertiary referral, and duration of follow up did not differ significantly (p>0.05). The majority of patients were referred by an ophthalmologist (358; 61%); 127 (22%) were referred by their primary health care physician and occasional patients were referred by the emergency department or other (non-ophthalmological) specialists within the hospital itself. The mean follow up period was 4-3 years.
The diagnostic criteria for uveitis were those defined by the International Uveitis Study Group. Scleritis (an ocular inflammatory process in the wall of the eye, which may extend to adjacent ocular tissues and cause uveitis) was considered as a distinct entity in the spectrum of intraocular inflammatory processes. All patients underwent a standard screening protocol which depended on the anatomical classification of the inflammatory process. Selected patients (depending on the history, character, and activity of their ocular disease as well as the outcome of the laboratory and radiographic screening procedures) underwent special tests and diagnostic procedures (“tailored approach”). These tests included HLA-A29 and HLA-B5 typing, radiography of the sacroiliac joints and skull, computed tomographic (CT), brain scanning, gallium-67 whole body scintigraphy, conjunctival and lacrimal gland biopsies, Mantoux test, serological tests for Toxoplasma and Borrelia, and aqueous or vitreous humour analysis for evidence of intraocular synthesis of specific antiparasitic and antiviral antibodies. Since the serological tests for Toxoplasma are positive for a considerable percentage of the general population and therefore are not indicative of active ocular involvement, the diagnosis of presumed ocular toxoplasmosis was based on the clinical observation of unilateral focal necrotising retinitis, sometimes associated with typical old pigmented scars. The diagnosis of sarcoidosis was always confirmed by histological examination of biopsy specimens. The diagnosis of ankylosing spondylitis was based on the criteria described by Bennet and Burch. All other systemic diseases were diagnosed according to current diagnostic criteria; the patients were also examined by the respective specialists. AIDS patients were not included in this study; because the tests for anti-human immunodeficiency virus (HIV) were not routinely performed, the number of eventually HIV infected patients without AIDS is not known.

The following data were recorded: sex and age of the patients, age at the onset of uveitis, referring physician, anatomical site and aetiological agent of uveitis, eventual associations with systemic diseases, all complications of uveitis and the subsequent treatment, and maximum visual acuity at the end of follow up.

Legal blindness was defined as a best corrected visual acuity of less than 0·1 for the better eye. This corresponds to the standard WHO definitions of severe visual impairment (equal to or better than 20/400 but less than 20/200) and blindness (from no light perception to 20/400). The criterion for visual impairment was a best corrected visual acuity equal to or less than 0·3 for the eye with better vision. To determine the visual loss, the final visual acuity was used and not the worst visual acuity at any visit. In patients with more than one complication, the cause of visual loss was attributed to the first complication which caused the final blindness or visual impairment (for example, first, toxoplasmic macular lesion followed by retinal detachment). Visual loss due to other causes which were not related to uveitis (for example, amblyopia) was not included in the final evaluation. However, the complications from the treatment for uveitis (for example, steroid induced cataract) were included.

Glaucoma was considered in the eyes with the combination of elevated intraocular pressure and visual field defects and not in cases with ocular hypertension only. The visual field loss from glaucoma resulting in less than 10 degree field was considered one of the criteria of legal blindness.

Cystoid macular oedema was defined by both clinical and angiographic criteria. Angiographic evidence was required in all cases where the cause of legal blindness of visual impairment was attributed to macular oedema.

We used the $\chi^2$ test for statistical analysis. A $p$ value of less than 0·01 was considered significant.

## Results

Within the group of 582 patients, 203 (35%) suffered from significant visual loss: bilateral legal blindness developed in 22 (4%), 26 (4·5%) had one blind eye with visual impairment of the other, and nine (1·5%) had bilateral visual impairment (Table 1). Unilateral visual loss occurred in 146 (25%), blindness in 82 (14%), and visual impairment in 64 (11%) patients.

In this patient series, anterior uveitis was the predominant anatomical diagnosis (246 cases; 42%); 129 (22%) presented with posterior uveitis, 107 (19%) with panuveitis, 78 (13%) with intermediate uveitis, and 22 (4%) with scleritis. When the patients were subdivided according to anatomical site, those with panuveitis had the worst visual prognosis; 9% of patients with panuveitis became legally blind and 19% suffered bilateral visual impairment (Table 1). Cystoid macular oedema developed in 22 (9%) patients with anterior uveitis, 32 (41%) with intermediate uveitis, 36 (28%) with posterior uveitis, 57 (53%) with panuveitis, and three (14%) with scleritis.

Cystoid macular oedema was the most frequent cause of both irreversible blindness and visual impairment: 33/152 (29%) of affected blind eyes and 46/113 (41%) of visually impaired eyes. In the majority of cases bilateral visual loss was caused by a combination of various complications, so that a different cause of the visual handicap could be determined for each eye. The most important cause of visual blindness was idiopathic macular oedema.
loss per eye was cystoid macular oedema followed by corneal opacities and macular inflammatory lesions. Causes of unilateral blindness and visual impairment, which were more consistent, included cystoid macular oedema, macular inflammatory lesions, retinal vascular abnormalities, and retinal detachment. Complications of uveitis were encountered in more than half of the patients; the distribution is given in Table 2.

In total, 136 (23%) patients required one or more intraocular surgical procedures. The percentage of those requiring surgery increased with the duration of follow up (Table 3). The most frequent surgical procedures were cataract extractions (n=76), vitrectomy (n=38), and surgery for glaucoma (n=25) and retinal detachment (n=16). Laser treatment (retina, iris, after cataract) was performed in 37 cases. Since the patients who developed cataract underwent extraction, this complication was not encountered as a cause of blindness, but ranked second as a cause of (temporary; waiting for surgery) visual impairment. Cystoid macular oedema was present in 32/76 (42%) patients after cataract surgery and 15/39 (39%) patients with a cataract still in situ. Glaucoma ranked third among the complications of uveitis; 25 of the 66 (38%) patients with uveitic glaucoma underwent surgery.

The most frequent systemic disorders associated with uveitis were sarcoidosis (n=56; 10%) and ankylosing spondylitis (n=20; 3.4%); an additional 43 patients had HLA B27 associated acute anterior uveitis without ankylosing spondylitis; the most common ocular disease was ocular toxoplasmosis (n=60; 10%; Table 4). The frequency of bilateral blindness and visual impairment among patients with uveitis of unknown aetiology did not differ significantly from that found for uveitis of known aetiology (blindness 5.5% versus 2.9%, p=0.1; visual impairment 7.5% versus 5.2%, p=0.3; Table 4).

Bilateral visual blindness or impairment occurred in uveitis of unknown origin in 42% (24/57) and 14% (8/57) of bilaterally blind patients had uveitis associated with (histologically confirmed) sarcoidosis (Tables 1 and 4). Uveitis in juvenile chronic arthritis had the worst visual prognosis; five out of eight patients suffered bilateral visual impairment or blindness. Of the 63 patients with HLA B27 associated acute anterior uveitis, none exhibited bilateral visual loss; there were three cases of unilateral blindness and three of unilateral impairment. Ocular toxoplasmosis was the most frequent cause of both unilateral legal blindness and unilateral visual impairment; this was attributed to the site of the retinal inflammatory lesion in the macula. None of the 60 patients with ocular toxoplasmosis experienced bilateral loss of vision. None of five patients with Behçet’s disease was bilaterally blind; however, three developed unilateral blindness.

### Table 2 Complications of uveitis (n=582)

<table>
<thead>
<tr>
<th>Complication</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Cystoid macular oedema</td>
<td>150</td>
</tr>
<tr>
<td>Cataract</td>
<td>115</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>66</td>
</tr>
<tr>
<td>Retinal vascular abnormalities</td>
<td>64</td>
</tr>
<tr>
<td>Macular lesion</td>
<td>30</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>26</td>
</tr>
<tr>
<td>Corneal opacities</td>
<td>24</td>
</tr>
<tr>
<td>Phthis</td>
<td>14</td>
</tr>
<tr>
<td>Optic nerve atrophy</td>
<td>13</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>42</td>
</tr>
</tbody>
</table>

*There were many patients with more than one complication: therefore the total number of patients is less than the total number of complications.

### Table 3 Surgery in uveitis

<table>
<thead>
<tr>
<th>Follow up</th>
<th>n</th>
<th>With surgery</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>&gt;1 Year</td>
<td>582</td>
<td>136</td>
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<tr>
<td>&gt;1 Year</td>
<td>430</td>
<td>125</td>
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<tr>
<td>&gt;2 Years</td>
<td>276</td>
<td>103</td>
</tr>
<tr>
<td>&gt;3 Years</td>
<td>219</td>
<td>89</td>
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</table>

### Table 4 Visual loss in uveitis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Bilateral legal blindness</th>
<th>Bilateral visual impairment*</th>
<th>Unilateral legal blindness</th>
<th>Unilateral visual impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA B27 positive acute anterior uveitis (n=63)</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Toxoplasmosis (n=60)</td>
<td>0</td>
<td>0</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Sarcoidosis (n=56)</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Fuchs’ cyclitis (n=31)</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Multifocal chorioretinitis (n=24)</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Juvenile chronic arthritis (n=8)</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Acute retinal necrosis (n=6)</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Birdshot retinochoroidopathy (n=5)</td>
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<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Behçet disease (n=5)</td>
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<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Sempigrous retinochoroidopathy (n=5)</td>
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<td>0</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Miscellaneous (n=119)</td>
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<td>6</td>
<td>19</td>
<td>13</td>
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<tr>
<td>Underdetermined (n=200)</td>
<td>11</td>
<td>13</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>Total (n=582)</td>
<td>22</td>
<td>35</td>
<td>82</td>
<td>64</td>
</tr>
</tbody>
</table>

*This group included 26 patients with a combination of legal blindness in one eye and visual impairment of the other (three with sarcoidosis, three with juvenile chronic arthritis, two with Fuchs’ cyclitis, one with acute retinal necrosis, and one with multifocal choroiditis, 16 with miscellaneous and undetermined conditions).

### Discussion

Within the group of 582 patients, 203 (35%) developed blind or visually impaired eyes. Bilateral loss of visual acuity developed in 10% and unilateral loss of vision occurred in an additional 25% of all patients with uveitis. The principal mechanism of visual loss in uveitis was cystoid macular oedema.

In the Netherlands, the patient is referred for either diagnostic or therapeutic help in the event of recurrent, chronic, or very severe acute uveitis. Acute cases which respond favourably to therapy are usually not referred. Although the results from two centres included did not differ significantly, the variability in timing of referral and the treatment given may have influenced the overall outcome and the findings should be interpreted with caution. The retrospective character of this study did not allow the clinically relevant evaluation of the relationship between the therapy data and visual prognosis.

Uveitis may be caused directly by various infectious agents; in the majority of such cases specific antimicrobial therapy is available. Uveitis may also be associated with diverse, usually idiopathic, systemic diseases (for
example, Behçet’s disease); the treatment strategies for these diseases are continuously being developed.15 The identification of a specific ocular disease (usually of unknown aetiology and without an underlying systemic disease — for example, Fuchs’ heterochromic uveitis, pars planitis) is important for the visual prognosis since information on clinical course, complications, and treatment regimens is then available. The surprising finding of the similarity in visual prognosis for patients with uveitis of established and undetermined origin is not easy to understand and certainly needs further study and evaluation.

Although cataract and glaucoma frequently complicated the course of uveitis (19% and 11%, respectively), their importance as a cause of the loss of optimal visual acuity remained limited. Cataract surgery in uveitic eyes may give rise to or exacerbate cataractous macular oedema.16 In this study, the frequency of cataractous macular oedema did not differ between patients who did or did not undergo cataract surgery. The design of our study, however, did not allow evaluation of the impact of cataract surgery on the increase in pre-existing macular oedema.

Of the systemic diseases, the most frequent cause of blindness was uveitis associated with sarcoidosis, especially in those suffering from panuveitis. The occurrence of blindness in at least one eye in 10% of the patients with sarcoidosis, as reported in an earlier publication, is supported by our results.17 18 The most frequent cause of unilateral loss of vision was ocular toxoplasmosis. There were no cases of bilateral blindness or visual impairment among the 60 patients with this disease. Studies on the visual outcome of ocular toxoplasmosis in large patient populations are not available and, therefore, the absence of bilateral visual loss in our patients cannot be compared with the results of other studies.19–21 Information on the long-term prognosis of ocular toxoplasmosis (especially the congenital type of the disease) is urgently needed, since preventive measures for congenital toxoplasmosis are vigorously recommended.22 23 HLA B27 associated uveitis was reported to have a favourable visual outcome despite the occurrence of posterior segment complications; none of our 63 patients suffered bilateral visual loss.24 25 The comparison of our data on the less frequent types of uveitis with previously published reports on one disease entity is very difficult. The poor visual prognosis for acute retinal necrosis, juvenile chronic arthritis, and serpiginous chorioretinopathy noted even for the small numbers of patients in our study was known from previous publications.26–29 All patients with acute retinal necrosis (n=6) developed visual loss (Table 4). Four of our five patients with serpiginous chorioretinopathy became blind or impaired. The long-term visual prognosis for birdshot retinochoroidopathy is not yet entirely clear: the disease has been reported to stabilise after the initial active stage while other series have demonstrated that 40% of the patients experienced a loss of useful vision in one or both eyes.30–32 There were no cases of bilateral blindness among five patients with Behçet’s disease (mean follow up of 5 years). Behçet’s disease has repeatedly been reported to have a poor visual prognosis although it seems that aggressive therapeutic management improves the long term visual outcome.33–35 The administration of aggressive cyclosporin A therapy in our cases may have improved our findings; however, it should also be noted that the number of patients was very small and our criteria for loss of visual acuity very strict.

Intermediate uveitis was complicated by cystoid macular oedema in 41% of the cases, which is in accordance with previous reports.36 37 When fluorescein angiography was performed repeatedly, the incidence of cystoid macular oedema in intermediate uveitis became even higher (65–79%).38 39 Nevertheless the impact of cystoid macular oedema on visual acuity remained limited and the visual prognosis for cystoid macular oedema in intermediate uveitis was much better than that for cystoid macular oedema and panuveitis (Table 1).

We conclude that cystoid macular oedema was the most frequent complication among patients with uveitis and its occurrence played a decisive role in the visual outcome. The best treatment for uveitic macular oedema has yet to be identified.40 The timing of eventual treatment of macular oedema in uveitis patients is difficult, because the loss of visual acuity is gradual and therapy may induce many systemic and ocular complications. Therefore, treatment is usually not initiated until late in the disease process but then the reversible stage of the disease may already have passed.41 The causes of blindness in the western World are probably changing as a result of recent advances in diagnosis and therapy of ocular and systemic diseases, epidemiological changes, and other factors. As a consequence there may be a growing impact of uveitis on blindness, especially in the younger age groups. Recent surveys of the causes of blindness which focus not only on the ocular features but also on the underlying primary conditions, such as uveitis, are needed.


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