PERSPECTIVE

The possible impact of uveitis in blindness: a literature survey

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The inflammatory process of the uvea is called uveitis and may cause sight threatening damage to the eye. The aetiological factor in about 30% of the cases of uveitis is unknown. If established clinical entities without known cause, such as Fuchs' uveitis, are included, no aetiological agent or association with systemic disease can be identified in about 50% of cases.¹ Uveitis may be induced by infection, autoimmune disease, trauma, or malignancy. It is recommended that the different forms of uveitis should be classified according to their anatomical localisation— anterior uveitis, intermediate uveitis, posterior uveitis, and panuveitis.^{2,3}

The uvea plays an important role in the ocular immunological defence mechanisms. Immunologically speaking the eye has a deviant and privileged position because of the blood-retina barrier, absence of lymphatic drainage, and a special feature called the anterior chamber associated immune deviation (ACAID). These special defence mechanisms contribute to the preservation of vision.⁴ If these defence mechanisms fail, intraocular inflammation will arise. Uveitis, mainly posterior uveitis, is an important cause of blindness, resulting in 10% of all cases of blindness.^{5,6}

Although uveitis is a well known cause of blindness, there is only scant knowledge concerning the prevalence and incidence of uveitis among the blind. In most epidemiological studies dealing with blindness, uveitis was not considered a distinct entity.⁷⁻¹³ The complications of uveitis—for example, cataract, secondary glaucoma, and macular abnormalities, are included in many epidemiological studies about blindness, but how many of these are actually attributable to uveitis is not specified.⁷ The largest population based study of the Western world, the Framingham Eye Study, illustrates this phenomenon: patients with blindness due to retinal toxoplasma lesions are classified as having macular degeneration; secondary cataract is indicated but carries no aetiological diagnosis—for example, uveitis, trauma.⁷ Proper population based studies on the extent of uveitis as a cause of blindness and visual impairment unfortunately do not exist, although such data would be a very beneficial contribution to our knowledge about uveitis.

Definitions

Blindness and low vision are always measured as the visual acuity of the better eye, since vision in this eye determines the actual maximum binocular visual acuity. Blindness is defined by the World Health Organisation (WHO) as the best possible corrected visual acuity in the better eye of less than 0.05 (20/400) or corresponding visual field loss of $\leq 10^\circ$. Severe visual impairment is defined as the best possible corrected visual acuity in the better eye of 0.05 (20/400) or more but less than 0.1 (20/200) (see Table 1).^{8,14,15}

Legal blindness is defined as the level of blindness that makes a person eligible for a reduction in tax and other

benefits in certain countries. In the USA and in most Anglo-American countries the threshold for this is 0.1 (20/200) or worse or a visual field $\leq 20^\circ$. Moderate visual impairment which makes the person eligible for educational assistance in the USA is defined as a visual acuity of 0.25 to 0.12 (20/70 to 20/160). For the purpose of this survey blindness was defined as visual acuity in the better eye of less than 0.05 (20/400) and visual impairment as 0.05 (20/400) or better but less than 0.1 (20/200).

Worldwide blindness is defined as all the blind people in the world. The Western world is defined as the established market economies—Western Europe and North America.

Prevalence is the number of cases, new and old, within a population with a certain disease existing at a given time and is usually expressed as a percentage. Exact prevalence numbers can only be obtained from population based studies. Incidence is the number of new cases of a condition that occur within a specified period of time and is usually expressed as a percentage or per 1000 of the population at risk.¹⁶

Causes of blindness worldwide

It was estimated in 1995 that 38 million people in the world are blind, 0.7% of the total population, while an additional 110 million people worldwide have visual impairment. By far the majority (75%) of worldwide blindness occurs in Africa and Asia, with the highest prevalence in sub-Saharan Africa where 1.4% of the total population is blind compared with, for instance, 0.3% in the Western world.⁸ Cataract is the leading cause of worldwide blindness followed by trachoma and glaucoma, accounting together for 71% of all blindness. If these figures are divided and analysed by economic region considerable differences are found. All treatable causes of blindness—for example, cataract and glaucoma, have a much lower frequency in the Western world; here, for example, cataract accounts for 3.5% of blindness, while this percentage is 57.6% in Latin America and the Caribbean.⁸ Naturally, these differences are explained by advanced surgical techniques and easier access to medical care.

The results of these studies on blindness in the Western world are difficult to interpret. Very often the classification of diseases is not consistent: anatomical diagnosis (for example, corneal opacities, cataract) and causal diagnosis (for example, onchocerciasis, trachoma) are used in one and the same system simultaneously. Thus, in most studies one entity may appear in different categories—for exam-

Table 1 Blindness defined as visual acuity in the better eye (adapted from Thylefors et al,⁸ Thylefors,¹⁴ and Simons¹⁵)

Blindness WHO	<20/400 (0.05)
Severe visual impairment WHO	$\geq 20/400$ and <20/200
	≥ 0.05 and <0.1
Legal blindness	$\leq 20/200$ (0.1)
	Visual field $\leq 20^\circ$

ple, uveitis and its various complications. Unfortunately, simultaneous classification using anatomical and causal diagnosis was recommended by the WHO.¹⁴ Therefore the comparison of results is often not possible.

Several studies have been conducted among the elderly and are either not representative population based sample surveys, or are based on hospital populations or government registered institutions for the blind, which have been shown to underestimate the number of blind people and specific causes of blindness.^{9 10 13 17} Prevalence statistics on the causes of blindness are actually available only from developing countries.¹⁶ The exact percentage of worldwide blindness due to uveitis and the impact of uveitis on worldwide blindness is unknown, owing to the problems in epidemiological statistics mentioned above.

Blindness in the Western world

In the Western world, blindness is mainly the result of disorders of the posterior segment of the eye as age-related macular degeneration and diabetic retinopathy. Both are associated with older age and account for 12% to 43% and 7% to 17% of all cases of blindness.^{11-13 18 19} As visual impairment due to diabetic retinopathy has become treatable because of increased screening and early treatment, its incidence has decreased relatively compared with age-related macular degeneration where, essentially, no treatment is available.^{11 12}

There are some differences reported about the prevalence of causes of blindness between the European countries and the USA.²⁰ As study designs are often different, the comparison of data is extremely difficult. Of special interest is the higher incidence of blindness among the black population in the USA, probably mainly the result of socioeconomic factors and the high incidence of glaucoma in this population group.²¹⁻²³ Recently, it has been reported that the prevalence of age-related macular degeneration may be less common in Europe than the USA.²⁴ It has been estimated that uveitis causes 10% of the cases of blindness in the USA, while European studies mention percentages of 3% to 7%.^{5 18 19 25}

Blindness in the developing countries

Many cases of blindness in the developing countries would essentially be treatable or preventable if the resources and staff were available. Much attention has been paid in ophthalmological discussions to cataracts in developing countries.^{26 27} But, in addition to surgical problems such as cataracts, one must not forget that many other ocular diseases in developing countries may be prevented (see Table 2).^{28 29} Prevention of these diseases is obviously a major problem, as they still have a high prevalence in developing countries. For example, the leading cause of world childhood blindness is vitamin A deficiency causing xerophthalmia, which accounts for 70% of 500 000 blind children every year.⁸ Infectious causes of keratitis and uveitis may be treatable and form a major problem in this part of the world. Trachoma alone accounts for one quarter of all the blind people in the world. This is also the case in onchocerciasis which ranks as the fourth cause of blindness worldwide and is mainly seen in sub-Saharan Africa.⁸ Visual loss in onchocerciasis is the consequence of inflammation of both the anterior and posterior segment. Prevention may be possible by the annual administration of ivermectin, and fortunately the number of infected patients is decreasing.^{28 30 31} Nevertheless, the number of blind people as a result of onchocerciasis (globally 360 000), one of the uveitis entities, indicates the tremendous portion of blindness caused by intraocular inflammation.⁸ An estimated 250 000 people in the world are blind because of the sequelae of leprosy, another infectious

Table 2 Major causes of blindness in the developing countries (adapted from Thylefors et al⁸)

1 Cataract*	14 000 000
2 Trachoma*	5 866 000
3 Glaucoma*	4 800 000
4 Onchocerciasis*	360 000

*Possibly treatable (that is, preventable).

disease.^{32 33} To illustrate the magnitude of this number the estimated number of world blindness due to diabetic retinopathy is also 250 000.³²

How many of the cases of cataracts, glaucomas, retinal and optic atrophies in the developing countries are secondary to uveitis is not precisely known. Several studies mention percentages of blindness due to uveitis as between 2.4 and 10%, excluding onchocerciasis.³⁴⁻⁴¹ In a recent study in west Africa, uveitis, including onchocerciasis, ranked as second cause of blindness accounting for 24%. Non-onchocercarial uveitis still ranked as the second cause with 10%.³⁹ Considering that onchocerciasis is ranked as the fourth single cause of blindness, one may extrapolate that if other infectious and inflammatory causes such as, for example, leprosy are added, uveitis may rank even higher than fourth in the developing world.

Blindness and age in the Western world

Most of worldwide blindness occurs in the elderly; 58% are estimated to be older than 60 years and 3.8% of blindness occurs in people younger than 14 years.⁸ In the Western world, all frequent causes of blindness are associated with increasing age (see Table 3). The blindness rate in 90-year-olds is twice that observed in 60-year-olds.^{13 20} Age-related macular degeneration is the leading cause of new cases of blindness in the USA, where it affects 8% to 20% of the people over the age of 65 and accounts for between a quarter and a half the cases of blindness.^{7 12 13 20 21 24 42 43} Cataract is still a major cause of worldwide blindness, accounting for 13% to 27% of all blind people, strongly increasing with age. Blindness from glaucoma is possibly preventable and is found to be the cause of 10% to 12% of blindness in the elderly.¹¹⁻¹³ Although the prevalence of diabetic retinopathy in this age group increases with age, this disease ranks as the fourth cause of blindness at 2% to 7% (see Table 3).^{7 11-13}

Blindness in children in the Western world is mostly seen in conditions that lead to blindness in very early childhood and about half of children are blind as a result of brain disorders. The major ocular causes are retinopathy of prematurity (20%), optic nerve atrophy (20%), congenital malformations, (15%) and tapetoretinal degenerations (10%) (see Table 4).⁴⁴⁻⁴⁷ The incidence of several of these is decreasing as a result of prevention, early treatment, and prenatal diagnosis.⁴⁷ Studies on the registration of blind people in a hospital population or blind registration studies have shown that the middle aged group represents about 26% to 32% of all the blind people in a Western population.^{12 19 21} Only a limited number of studies report data on specific age groups other than the elderly or children. Reported diseases that cause blindness at a younger age than 65 years included accidents, optic nerve atrophy, tapetoretinal degeneration, congenital anomalies, and toxic damage including retinopathy of prematurity and

Table 3 Major causes of blindness of the elderly in the Western world (adapted from Leibowitz et al,⁷ Aclimandos et al,¹¹ and Tielsch et al¹³)

1 Age-related macular degeneration	40%
2 Cataract*	20%
3 Glaucoma*	11%
4 Diabetic retinopathy*	5%

*Possibly treatable (that is, preventable).

Table 4 Major causes of blindness in children in the Western world (adapted from Schmidt et al,⁴⁴ Drews et al,⁴⁵ and Goggin and O'Keefe⁴⁶)

1 Retinopathy of prematurity*	20%
2 Optic nerve atrophy	20%
3 Congenital malformations	15%
4 Tapetoretinal degeneration	10%

*Possibly treatable (that is, preventable).

Table 5 Major causes of blindness in the middle age group in the Western world (adapted from Nussenblatt,⁵ Thompson et al,¹² Krumpaszky and Klaus,¹⁹ and Makabe et al²⁵)

1 Tapetoretinal degeneration	20%
2 Congenital anomalies (including high myopia)	20%
3 Diabetes*	20%
4 Accidents*	5%
5 Uveitis*	10%

*Possibly treatable (that is, preventable).

diabetes. The mean blinding age is 65 for diabetic retinopathy and 73 for glaucoma.²⁵ The prevalence data reported are variable, but give more or less consistent figures about tapetoretinal degeneration and diabetic retinopathy in middle age with up to 20% and 20% respectively (see Table 5).^{12 19 25}

Economically speaking, the middle aged group (aged 20 to 65 years) is the most important as it includes the working age range. For many causes of blindness in this group no definitive cure is available. As Table 5 indicates, the blindness in adults in middle age that is caused by treatable diseases narrows down essentially to two large entities: diabetic retinopathy and uveitis accounting for about 20% and 10% respectively.^{5 12} The main cause of blindness in diabetes is not proliferative retinopathy any more but macular oedema occurring in exudative diabetic retinopathy.⁴⁸⁻⁵⁰ Thus, blindness due to diabetes will probably decrease in the younger age group, while it is expected to increase despite treatment in the older age group because of a proportionally larger increase of patients living longer with diabetes mellitus and a higher incidence of macular oedema.^{51 52} As mentioned earlier, only a few studies describe the causes of blindness in the middle aged adult. This is astonishing as it has been reported that 97% of the annual federal budgetary costs of blindness in the USA is spent on blind people in the adult group of working age.⁵³

Uveitis as a cause of blindness in the Western world

The sequelae of uveitis that may cause visual impairment are well known and include cataract, glaucoma, band keratopathy, vitreous opacities, retinal scars, retinal detachment, retinal vascular abnormalities, cystoid macular oedema, and optic atrophy. Several of these are surgically treatable, such as cataract and glaucoma.⁵⁴ There are no studies on the incidence of these vision threatening complications in uveitis, so the impact of therapy and prevention of visual loss in uveitis still remains unclear.

Blindness due to uveitis is usually not reflected in results reported on epidemiology of blindness and only few data are available about its incidence. It is estimated that it causes 10% to 15% of all cases of total blindness in the USA.⁵⁶ The percentage of blindness in the Western world that was attributed to uveitis was similar in those studies where uveitis was reported, and varied from 3% to 7% of the total blindness. As these studies do not include all uveitis cases and do not report separately on the complications of uveitis, such as cataract and glaucoma, this percentage is probably higher.^{18 19 25}

The prevalence of uveitis in Western countries has been reported as 38 per 100 000 and the incidence is about 14 to 17 per 100 000 of the population.⁵⁵⁻⁵⁹ Several reports on

the frequency of the different types of uveitis use the classification of the international uveitis study group and show similar proportions of anatomical entities.^{2 3 56 60} Most uveitis patients present at an age when they are in the most active period of their working life; approximately 70-90% are between 20 and 60 years old. In about half the patients the age of onset is in the third or fourth decade of life.^{2 6 56 60 61-63} This age distribution makes uveitis one of the ocular diseases with an important socioeconomic impact.

No major difference in the causes of uveitis could be found when comparing a British with an American population. This study did not include any patients with presumed ocular histoplasmosis, a disease mainly seen in the USA.⁶⁴ Naturally, there are demographic and genetic factors influencing the frequency of several diseases (for example, Behçet's disease and Vogt-Koyanagi-Harada syndrome).^{57 61 65} In studies that describe the changes of frequency of potentially blinding diseases in past decades, the relative part played by uveitis is still essentially the same.^{18 25 44} None of these studies as yet included patients with more recent uveitis entities such as cytomegalovirus retinitis and acute retinal necrosis, two entities with a poor prognosis that will influence the number of blind cases due to uveitis.

Uveitis patients often do not suffer from ocular disease alone; approximately 25% to 50% have an underlying systemic disease.^{2 60} It is not known exactly how many of the uveitis patients suffer from blindness or visual impairment; one study mentions a loss of 25% visual acuity in 4% of patients with anterior uveitis, 43% with posterior uveitis, and 40% with panuveitis.⁶⁶ Another recent study reports on 35% visual impairment or blindness, mainly due to posterior uveitis, with cystoid macular oedema as a leading cause.⁶⁷

Many data are available on the prognosis of visual acuity of specific aetiology. Acute anterior uveitis, accounting for at least 30% of all uveitis cases, has a good prognosis and leads to visual impairment in only 1% of the patients, whether it is associated with HLA B 27 or not.⁶⁸ Toxoplasmosis is the aetiological factor in about 10% of all uveitis patients and occurs mainly in young adults; it leads to severe visual impairment or blindness as a result of the central localisation of the lesion in at least 9% of the eyes affected.^{69 70} Ocular sarcoidosis accounts for up to 9% of all uveitis patients and causes blindness in at least one eye in 10%.⁷¹ Several forms of posterior uveitis and panuveitis are rare in the Western world but have a poor visual prognosis—for example, Behçet's disease, acute retinal necrosis, serpiginous chorioretinopathy, and cytomegalovirus retinitis.⁷²⁻⁷⁵

Of special interest is blindness in patients with acquired immunodeficiency syndrome (AIDS), which is still increasing and is almost always due to viral uveitis. Cytomegalovirus retinitis will develop in 20% to 34% of patients with AIDS. Untreated, it will lead to blindness within several months.⁷⁵ Owing to failure of virostatic treatment to control the disease, the retinitis recurs in the majority of patients. As improved therapy leads to longer survival in AIDS patients, it can be expected that the number of blind AIDS patients will increase.⁷⁶

Socioeconomic impact of blindness due to uveitis

In the USA the estimated federal budget costs for a blind person in the working age group—excluding costs for medical care, but including all state benefits, etc, amount to \$12 000 per person year.⁵³ It is reported that in the USA alone 1.1 million are legally blind, 337 000 of them in the age group between 20 and 65 years. It is estimated that in the USA alone 2.3 million suffer from uveitis and that uveitis causes 10% of the blindness encountered.^{77 78} If one

assumes that the value of 6% of the epidemiological studies is the baseline for middle aged people blinded by uveitis—which is probably an underestimate—this amounts to 20 220 blind people with a total of annual costs for this group of about \$242.6 million in the USA alone. A similar calculation for diabetic patients in this age group adds up to 242.7 million in the USA.⁵³ Taking into account the facts that many uveitis entities are curable and that its damage may be prevented or limited if treated early and adequately, further investment—whether financial, medical, or research—can be said to be valuable for the patient as well as the budget of the community.

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