Retinal detachment and herpesvirus retinitis in patients with AIDS

J G F Dowler, H M A Towler, S M Mitchell, R J Cooling, S L Lightman

Abstract

Background—The prolongation of survival of patients with herpesvirus retinitis and AIDS has been associated with a rise in the incidence of retinal detachment. In such cases, however, retinal reattachment may be difficult to achieve, and postoperative visual acuity may be poor despite anatomically successful surgery. Methods—In order to examine factors affecting the visual outcome of surgery, a retrospective review of 29 patients with retinal detachment, herpesvirus retinitis, and AIDS was performed. Retinal reattachment surgery (32 procedures) or prophylactic laser demarcation (five procedures) was performed in 28 eyes of 23 patients.

Results—The macula was attached in 23/28 (82%) eyes at the last outpatient visit. Best postoperative visual acuity (median 6/18, range 6/6–hand movements) was significantly greater than final postoperative acuity (median counting fingers, range 6/6–no perception of light) (Wilcoxon sign rank test, p=0.003), and was retained for a median of 3 months (1–91 weeks) after surgery. Poor visual outcome as evidenced by submedian final visual acuity was invariably associated with persistence of macular detachment, and significantly associated with the occurrence of optic atrophy (odds ratio=5, p=0.02).

Conclusion—Retinal reattachment surgery appears justified in patients with herpesvirus retinitis and AIDS, but postoperative visual deterioration may occur in association with optic atrophy.


Cytomegalovirus (CMV) retinitis affects 25–40% of patients with AIDS and represents the commonest ocular infection in these patients. Mean life expectancy following diagnosis of CMV retinitis, currently 8–12 months, has increased considerably since the start of the AIDS epidemic. Retinal detachment is reported to affect 18–29% of patients with CMV retinitis and AIDS, but the incidence increases with survival and may reach 50% 1 year after diagnosis of retinitis. Acute retinal necrosis due to varicella zoster virus (VZV) infection may further add to the morbidity associated with retinal detachment in patients with AIDS.

Retinal reattachment surgery in the context of necrotising herpesvirus retinitis in AIDS may prove technically difficult owing to the nature and location of retinal breaks, the evolution of new breaks, and the presence of incomplete posterior vitreous detachment. In eyes where retinal reattachment has been achieved, visual recovery may be impaired by recurrent retinitis or optic neuropathy. It is therefore relevant to consider what factors affect the visual outcome of retinal reattachment surgery in these patients, and whether such intervention is justified. In an attempt to answer these questions, findings relating to patients with retinal detachment, herpesvirus retinitis, and AIDS were analysed.

Patients and methods

A retrospective review was undertaken of patients with herpesvirus retinitis and AIDS under the care of the Vitreoretinal Surgical Unit and Acquired Immune Deficiency Clinic of Moorfields Eye Hospital in whom rhegmatogenous retinal detachment was diagnosed between July 1987 and July 1993. Twenty nine patients were included in the study; six patients with a postoperative follow-up of less than 6 weeks who did not die during that period were excluded. Twenty seven patients were male and two female; ages ranged from 27 to 59 (median 40) years. Bilateral retinitis was present in 15 patients, 12 of whom (80%) developed bilateral retinal detachment. Seven of these had bilateral retinal detachments at presentation, and the remaining five presented with unilateral detachment and subsequently developed detachment in the fellow eye. Diagnosis of CMV or VZV retinitis was based on clinical appearances supplemented in six patients by identification of viral DNA in vitreous fluid using molecular techniques based on the polymerase chain reaction. Retinitis was treated with standard induction and maintenance doses of ganciclovir or foscarnet for CMV retinitis, and acyclovir for VZV retinitis. Combination therapy or the intravitreal route was used in patients with CMV retinitis suffering systemic side effects of medication. Antiviral therapy was not modified in the immediate postoperative period except in response to changes in retinitis activity or the occurrence of drug related side effects.

Retinal reattachment surgery was undertaken in patients who were deemed likely to survive general anaesthesia and the early postoperative period, and in eyes in which there was evidence of good visual acuity or visual field in the recent past. Surgery was not undertaken in eyes with extensive active retinitis, marked optic atrophy, or retinitis involving the majority of the posterior pole unless severe...
Table 1  Intervals in months between diagnoses of AIDS, herpesvirus retinitis (retinitis), and retinal detachment (detachment), given as median (range), with significance values (p) for Wilcoxon rank sum comparison of medians

<table>
<thead>
<tr>
<th></th>
<th>All (0-89)</th>
<th>CMV (0-89)</th>
<th>VZV (0-89)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS to retinitis</td>
<td>10</td>
<td>14</td>
<td>1</td>
<td>0.02</td>
</tr>
<tr>
<td>AIDS to detachment</td>
<td>17 (0-91)</td>
<td>22 (2-91)</td>
<td>3 (0-10)</td>
<td>0.01</td>
</tr>
<tr>
<td>Retinitis to detachment</td>
<td>5 (0-12)</td>
<td>3 (0-8)</td>
<td>5 (0-12)</td>
<td>ns</td>
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</table>

All=all patients; VZV=patients suffering from varicella zoster virus infection; CMV=patients suffering from cytomegalovirus infection.

Table 2  Median interval to death (months) after diagnoses of AIDS, herpesvirus retinitis (retinitis), and retinal detachment (detachment), with significance values (p) for Mantel Haenszel comparison of survival curves

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>CMV</th>
<th>VZV</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>From diagnosis of AIDS</td>
<td>35</td>
<td>35</td>
<td>18</td>
<td>0.04</td>
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<tr>
<td>From diagnosis of retinitis</td>
<td>15</td>
<td>15</td>
<td>16</td>
<td>ns</td>
</tr>
<tr>
<td>From diagnosis of detachment</td>
<td>9</td>
<td>9</td>
<td>8</td>
<td>ns</td>
</tr>
</tbody>
</table>

All=all patients; VZV=patients suffering from varicella zoster virus infection; CMV=patients suffering from cytomegalovirus infection.

bilateral visual impairment was present and retinal reattachment offered the only prospect of retaining useful vision. Surgery was not undertaken in six patients because of a poor ocular or systemic prognosis. All procedures with the exception of laser demarcation were carried out under general anaesthesia.

Thirty two retinal reattachment procedures and five laser demarcations were performed in 28 eyes of 23 patients; 23 eyes were diagnosed as CMV retinitis (CMV group) and five as varicella zoster related retinitis (VZV group). Two of seven patients with bilateral retinal detachments at first presentation underwent retinal reattachment surgery to both eyes, four underwent surgery to one eye, and one patient was not offered surgery. Three of five patients developing sequential bilateral retinal detachments underwent retinal reattachment surgery to both eyes, and two patients underwent surgery to one eye only.

Extramacular detachments due to one or two retinal breaks with normal tissue between the macula and the detachment were demarcated with a triple row of argon laser burns (five procedures in five patients). One or two anterior retinal breaks within one quadrant were treated with scleral buckling; buckles were applied to support breaks but were not applied to areas of retinitis in which no breaks had been identified (three procedures in three patients). In the event of failure of these treatment modalities, or with multiple, posterior, or widespread breaks vitrectomy with gas (three procedures) or silicone oil injection (26 procedures) was undertaken. An explant was applied to 7/29 eyes undergoing vitrectomy, and inferior retinotomy with a triple row of argon laser burns was undertaken in those eyes to which an explant was not applied. Lensectomy was not performed. During vitrectomy in eyes in which posterior vitreous detachment was incomplete before surgery, dissection of the posterior hyaloid membrane was generally attempted but not invariably achieved. After vitrectomy with silicone oil injection, cataract surgery was undertaken in two eyes and removal of oil in one eye.

The following data were collected:
1. date of birth, date of diagnoses of AIDS, retinitis and each retinal detachment, date of death;
2. absolute CD4 lymphocyte counts (×10^9/l) at diagnosis of first retinal detachment;
3. visual acuity, retinitis activity, severity of optic atrophy (absent/moderate/marked) at diagnosis of each retinal detachment and at last review;
4. attributes of retinal breaks, grade of proliferative vitreoretinopathy and macular attachment status at diagnosis of each retinal detachment;
5. nature of operative or prophylactic intervention, postoperative visual acuity, and anatomical result.

**STATISTICAL ANALYSIS**

Medians of unpaired samples were compared using the Wilcoxon rank sum test; and paired samples using the Wilcoxon sign rank test. Proportions were compared using Fisher's test of exact probability. Kaplan-Meier product limit estimations were used to calculate survival; different groups were compared using the Mantel Haenszel (log rank) test. Cox's proportional hazards regression was used to evaluate survival controlling for covariates. Logistic regression was used to identify factors influencing the probability of submedian final visual acuity.

**Results**

**DISEASE COURSE**

The time course of disease and intervals to death are detailed in Tables 1 and 2. Intervals from diagnosis of AIDS to diagnosis of retinitis and first retinal detachment were greater in the CMV group than the VZV group. Survival following diagnosis of AIDS was significantly shorter in the VZV group than the CMV group (Fig 1). Absolute CD4 lymphocyte count (overall median 9 (×10^9/l), range 3–30) was similar in the CMV group (median 13 (×10^9/l), range 6–30) and VZV groups (median 9, range 3–16) (Wilcoxon rank sum p=0.26) and was not predictive of the interval from diagnosis of first retinal detachment to death (Cox proportional hazards regression p=0.97). The interval from diagnosis of first
retinal detachment to death in patients undergoing surgery (median 9 months) was longer than in unoperated patients (median 3 months) (Mantel Haenszel p=0.001) (Fig 2).

FEATURES OF RETINAL DETACHMENTS
Retinal breaks identified before intervention were small in 26/28 (93%) operated eyes, multiple in 17/28 (61%), and present in several quadrants in 10/28 (36%); they were often posteriorly located and occurred within areas of inactive retinitis or at the margins of such areas. Retinitis was inactive at the time of diagnosis of retinal detachment in 20/28 eyes (71%) and extended anterior to the equator in all cases; the associated chorioretinal adhesion modified the distribution of subretinal fluid. Incomplete posterior vitreous detachment was typical. Proliferative vitreoretinopathy of grade C1 or greater was present in 1/28 (4%) of initial detachments and 4/15 (27%) of redetachments (Fisher’s exact test, p=0.04). Breaks were present in the inferior quadrant (between 4.30 and 7.30 o’clock) in 12/28 (43%) of initial detachments and 11/15 (73%) of redetachments (Fisher’s exact test, p=0.11). Macular detachment was present in 13/28 (46%) of initial detachments, and with redetachment had occurred at some point in 18/28 (64%) eyes. Moderate optic atrophy was present in 2/28 (7%) eyes before surgery.

ANATOMICAL RESULTS
Thirty two retinal reattachment procedures and five laser demarcations were undertaken in 28 eyes of 23 patients. Subretinal fluid transgressed laser demarcation lines in three eyes; two subsequently underwent vitrectomy with silicone oil injection, and one underwent no further intervention. Scleral buckling failed to arrest the accumulation of subretinal fluid in two eyes, both of which subsequently underwent vitrectomy with silicone oil injection. At the last visit the macula was attached in 23 eyes (82%). Localised peripheral detachments were present in five of these eyes – two after successful laser demarcation and three after vitrectomy with silicone oil injection.

Macular attachment rates in this study are compared by treatment modality with published series in Table 3. The macula was attached at last review in 4/5 eyes in which application of an explant was combined with vitrectomy with silicone oil injection, and in 0/21 eyes undergoing vitrectomy, silicone oil injection, and laser without the application of an explant (Fisher’s exact test, p=1). Macular attachment rates were similar in the VZV group (4/5, 80%) and the CMV group (19/23, 83%) (Fisher’s exact test, p=1).

VISUAL ACUITY
Final visual acuity in the better seeing eye of patients with bilateral retinal detachment (median 6/60, range 6/6–no perception of light) was worse than in the unaffected eye of patients with unilateral retinal detachment (median 6/6, range 6/6–6/36) (Wilcoxon rank sum p=0.004), but no different from that in the affected eye (median 6/60, range 6/6–no perception of light) (Wilcoxon rank sum p=0.95). Similarly, final visual acuity in the better seeing eye of patients with bilateral retinitis was poorer (median 6/18, range 6/6–no perception of light) than in the unaffected eye of patients with unilateral retinitis (median 6/6, range 6/6–6/36) (Wilcoxon rank sum p=0.01), but no different from that in the affected eye (median 6/60, range 6/6–no perception of light) (Wilcoxon rank sum p=0.64).

Visual acuity before surgery (median 6/18, range 6/6–perception of light) did not differ significantly from best postoperative acuity (median 6/18, range 6/6–hand movements) (Wilcoxon sign rank p=0.59); however, final acuity (median counting fingers, range 6/6–no

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Comparison of macular attachment rates (macula) and total retinal attachment rates (total) in current series by treatment modality with total attachment rates in other published series (other)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (%)</td>
<td>Macula (%)</td>
</tr>
<tr>
<td>Vitrectomy and silicone oil</td>
<td>15/26 (58)</td>
</tr>
<tr>
<td>Vitrectomy and gas</td>
<td>2/3 (67)</td>
</tr>
<tr>
<td>Scleral buckling</td>
<td>1/3 (33)</td>
</tr>
<tr>
<td>Laser demarcation</td>
<td>2/5 (40)</td>
</tr>
</tbody>
</table>

Figure 2 Interval to death following the diagnosis of retinal detachment between patients who underwent surgery (operated patients) and those who did not (unoperated patients) because of a poor ocular or systemic prognosis.

Figure 3 Comparison of preoperative visual acuity with best postoperative visual acuity (VA) and final visual acuity in operated eyes.
perception of light) was worse than best postoperative acuity (Wilcoxon sign rank p=0.003) (Fig 3). Best postoperative acuity was retained after surgery for a median of 3 months (range 1–91 weeks) in eyes in which the macula was reattached; 50% of such eyes achieved best postoperative acuity at the last visit. Monocular visual acuity deteriorated between first and last visits by a median of 2 lines (range 4 lines of improvement to 7 lines of deterioration). No difference between CMV and VZV groups was identified in initial, best postoperative, or final acuity (Wilcoxon rank sum p=0.4, 0.23, 0.45 respectively).

Optic atrophy developed in 12/28 (43%) of eyes postoperatively, being moderate in three and marked in nine (Fig 4). No association could be identified between the development of optic atrophy and either postoperative reactivation of retinitis or failed retinal reattachment (Fisher’s exact test, p=0.7, 0.3 respectively). Optic atrophy developed in 4/5 eyes in the VZV group and 9.23 eyes in the CMV group (Fisher’s exact test, p=0.62). Postoperative reactivation of retinitis occurred in 12/28 (43%) eyes; the macula being involved de novo in two eyes.

To identify factors predisposing to a poor visual outcome, defined as final visual acuity less than median, a multiple logistic regression model was formulated. Postoperative persistence of macular detachment was invariably associated with a poor visual outcome, and the presence of moderate or marked postoperative optic atrophy was associated with an increased risk of submedian final acuity (odds ratio =5, p=0.02). Postoperative reactivation of retinitis, the nature of the pathogen, and prior macular detachment were not associated with an increased risk of poor visual outcome.

Discussion
The prolongation of survival of patients with herpesvirus retinitis and AIDS has been associated with a rise in the incidence of retinal detachment. This growing problem is compounded by technical difficulties in retinal reapposition and concerns that postoperative visual deterioration may occur despite a satisfactory surgical outcome. Decisions to undertake surgical intervention must take account of the visual potential of the affected eye and the condition of the fellow eye, as well as the patient’s systemic condition and life expectancy.

The median interval to death after diagnosis of first retinal detachment was 9 months in this series, which, compared with the published range of 3–9 months, reflects the trend towards prolongation of survival in these patients. The short interval from diagnosis of first retinal detachment to death in patients in whom surgical intervention was not undertaken because of poor systemic or ocular prognosis (3 months) reinforces the importance of careful patient selection. Although results of subgroup analysis should be interpreted with caution because of small sample size and the retrospective nature of the study, it was notable that survival from diagnosis of AIDS in patients with CMV was approximately twice as long as in patients with VZV, and the intervals from diagnosis of AIDS to diagnosis of retinitis or retinal detachment reflected this. The interval from diagnosis of first retinal detachment to death did not, however, differ significantly between the CMV and VZV groups, suggesting that patients with VZV infection reached an advanced stage of disease more rapidly than those with CMV infection. This concept is reinforced by the generally low level of CD4 lymphocyte counts (range 3–30 ×10⁶/l) and the absence of a significant difference in CD4 counts between the VZV and CMV groups.

Retinal detachment in these patients showed characteristic features. Retinal breaks were frequently small, multiple, posteriorly located, and associated with areas of retinitis. Pre-equatorial retinitis, a recognised risk factor for retinal detachment, was universal. It has been suggested that retinal break formation, both in the context of retinal detachment and redetachment, may be related to active retinitis. This was not the case for the majority of eyes in this series, a finding which accords with a growing consensus that retinal breaks evolve within areas of inactive retinitis or at the margins of such areas.

At the last visit, the macula was attached in 82% of operated eyes. The spread of subretinal fluid was limited by laser demarcation in only two of five eyes; this is in accord with observations from other studies that subretinal fluid may transgress laser demarcation lines. Scleral buckling procedures permitted retinal reattachment in one eye of three, redetachment arising in the two remaining eyes from unrecognised or evolving breaks in areas of retinitis unsupported by the explant. It has been suggested that if a scleral buckle is applied, it should support the entire area of retinitis rather than being limited to the location of identified retinal breaks, as in this study. Such an
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... approach would, however, limit the use of scleral buckling to retinal detachment associated with a small total area of retinitis, a relatively uncommon scenario.6

Macular attachment rates were highest with vitrectomy procedures, as in other series.4 5 10-18 Silicone oil injection is of particular value in the tamponade of posterior, multiple, widespread, or evolving breaks, and in the management of proliferative vitreoretinopathy. Tamponade of inferior retinal breaks may, however, be difficult to achieve;11 12; in this series 73% of redetections were related to such breaks, and inferior subretinal fluid persisted in three eyes. An adjunctive encircling scleral buckle supports inferior breaks in addition to lessening oil induced hypermetropia,11 but if buckle height diminishes after surgery, a relative oil underfill may occur,12 and it may be more appropriate to attempt to achieve a ‘complete oil fill’ supplemented with laser demarcation and no explant.13 In the present series there was no difference in reattachment rate for vitreectomy/oil procedures between those employing scleral buckling and those not. Redetections were more frequently associated with proliferative vitreoretinopathy than initial detachments, which may reflect difficulties in inducing complete posterior vitreous detachment at the time of surgery with contraction of remnants of attached posterior hyaloid. Additional complications of vitreectomy with silicone oil injection include refractive difficulties owing to induced hypermetropia and reduced accommodative amplitude,11 and the development of cataract and other silicone oil related morbidity in the longer term.5 11 13

More than half the patients had bilateral retinitis, and of these 80% developed bilateral retinal detachment. Bilaterality of retinitis and retinal detachment were associated with a significantly poorer visual acuity in the better eye at the last visit. Patients with bilateral retinitis are at particular risk of severe binocular visual loss, and retinal reattachment surgery may therefore be appropriate in these patients where the ocular prognosis would deter the surgeon from such intervention in a patient with unilateral retinitis.

In the current series half the patients experienced some postoperative visual deterioration even in eyes in which the retina was attached. However, useful visual acuity, not significantly different from initial acuity, was retained on average for 3 months after surgery. These findings, together with the association of poor visual outcome with failed retinal reattachment, suggest that surgical intervention conferred some benefit, albeit for a limited time. Patients should, however, be warned of the risk of late postoperative visual deterioration, even after anatomically successful surgery with satisfactory postoperative visual acuity in the early postoperative period.

The mechanisms of visual deterioration following retinal reattachment surgery in patients with herpesvirus retinitis and AIDS are unclear. Postoperative reactivation of retinitis with macular involvement was identified in a recent study16 as the major cause of postopera-

tive visual deterioration, affecting 15/65 eyes. In the present series, however, reactivation of retinitis occurred in only two eyes and was not predictive of poor visual outcome. Optic neuropathy may also give rise to postoperative visual deterioration, but may be difficult to diagnose in the presence of retinal detachment and inflammation, even given specific diagnostic criteria.20 This difficulty may account for the variation in reported incidence (14-95%).4 13 14 16 Optical atrophy may be recognised with greater certainty, although its cause may be difficult to determine; possibilities include viral optic neuritis,20-23 the secondary effects of retinitis,16 ocular hypoperfusion,14 silicone oil toxicity,24 and persistent retinal detachment. In the current series optic atrophy was associated with an increased risk of a poor visual outcome (odds ratio = 5, p = 0.02). No relation was identified between the development of optic atrophy and failed retinal reattachment, the identity of the pathogen, or postoperative reactivation of retinitis. This parallels findings in a recent study of patients with CMV retinitis and AIDS in which only 25% of optic atrophy could be accounted for by the observed extent of retinitis following retinal detachment surgery.16 The cause of optic atrophy in these patients remains obscure, but an inability to correlate the severity of other pathological processes with the extent of optic atrophy may indicate that a primary optic neuropathy, such as neuritis due to CMV or VZV,20-23 is involved.

On the basis of our findings, we recommend that surgery for retinal detachment caused by herpesvirus retinitis in AIDS be undertaken in those patients in which the ocular and systemic prognosis appears acceptable, particularly if retinitis is bilateral. Vitrectomy surgery offers the most effective means of securing or retaining macular attachment. Useful vision may be retained for some time after surgery, but may deteriorate in the presence of optic atrophy. Further study might usefully be directed at elucidating the pathogenesis of optic atrophy in this context.

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