SCIENTIFIC REPORT

Ocular complications in heart, lung and heart-lung recipients

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Aim: To prospectively assess ocular morbidity and the need for ocular screening in patients on long term, high dose immunosuppression for the maintenance of solid organ transplants.

Methods: Dilated ocular examinations were performed on patients receiving immunosuppression for the maintenance of heart, lung and heart-lung transplants. Patients were examined repeatedly in the post transplant period.

Results: Of the 115 transplant recipients examined 62 (54%) had ocular findings. The most common findings were cataracts (17% of those examined) followed by hypertensive change (8%), chorioretinal scarring (5%) and diabetic retinopathy (3%). One patient developed ocular infective complications following surgery due to *Aspergillus spp.* endophthalmitis. 18 patients (16%) were symptomatic at examination with the most common symptom being blurred vision. The most common finding in symptomatic patients was cataract with almost a quarter of patients having posterior subcapsular lens opacity that could be attributed to steroid therapy.

Conclusion: Patients had surprising low incidences of ocular infective complications despite previous reports. It is likely that this is due to improved immunosuppression regimes and improved monitoring of immunosuppression in the early post-transplant period. The screening of asymptomatic individuals following heart, lung or heart-lung transplantation was not supported by this study.

Solid-organ transplantation requires immunosuppressive agents in large quantities and at high doses. Complications of this immunosuppression are common and generally managed by monitoring for end organ toxicity and drug levels. It has been suggested that ocular examination should be routine following transplantation in order to identify complications before sight-threatening lesions occur. Ocular complications may affect quality of life after recovery so as survival improves it becomes increasingly important to identify and aggressively treat them.

Infections account for 18–20% of all mortality in transplant recipients.¹ Since infection may be allograft or life threatening it is managed with a high index of suspicion and an arsenal of prophylaxis, pre-emptive and therapeutic treatment.² A number of the infections characteristic of immunosuppression have typical ocular manifestations. In addition to opportunistic infection ocular complications following transplantation may be non-infectious complications secondary to drug toxicity or non-infectious complications associated with underlying disease processes such as diabetes or hypertension.

No laboratory indices will give a direct indication of end-organ toxicity in the eye so disease presents only when sufficient to cause ocular symptoms or when detected by screening. A retrospective audit of ocular complications following heart, lung, heart-lung and liver transplantation by Ng and colleagues³ found that these occurred in 2% of patients and 58% of complications were opportunistic infections. Herpes

group viral retinitis (42%) and fungal chorioretinitis (11%) were the most common complications reported. They note that this is an underestimate of the problem as only symptomatic patients were identified. Ocular symptoms may be ignored and remain unreported as they have relatively minor consequences to the patient in the immediate post-transplant period, particularly if transitory.⁴ Screening would allow for the early identification of disease as well as potentially having the further advantage that accurate ocular diagnosis may sometimes offer clues to as yet undiagnosed co-existing systemic infections.

METHODS

Patient selection

Following local ethics committee approval and written informed consent ocular examination was offered to all patients attending a post-transplantation outpatient clinic. In-patients were also invited for assessment if they were able to tolerate examination. Repeat examinations were encouraged if symptoms occurred or when patients were attending follow-up visits in the transplant clinic.

Data collected

The following variables were recorded for each patient: age, gender, date and type of transplant, Cytomegalovirus (CMV) serologic status of donor and recipient prior to transplant, number of rejections (in the previous 3 months) immunosuppressive therapy, previous CMV infection. Ocular assessments were performed in the outpatient department and consisted of history and examination with visual acuity, slit lamp examination, biomicroscopy with a 78D lens and indirect ophthalmoscopy with a 28D lens.

RESULTS

115 heart, lung and heart-lung transplant recipients were examined. 78 heart, lung or heart-lung transplants were performed at Harefield Hospital during the study period (1st June 1999–1st September 2000). Ocular examination was performed 0 to 1300 weeks (25 years) after transplantation (median 43 weeks). The median age of patients was 51 (range 16–70 years). There were 78 males and 37 females.

Most patients were managed on regimes involving corticosteroids, azathioprine and cyclosporine. A minority of patients were managed on tacrolimus (Tac) or mycophenolate mofetil (MMF) containing regimes. Patients were on anti-microbials including septrin, nystatin, itraconazole and acyclovir as required. CMV negative recipients were treated prophylactically with high dose oral acyclovir. CMV antigenaemia was routinely measured in CMV negative patients and treated with IV ganciclovir in the presence of symptoms or other evidence of CMV disease.

A lung recipient with a pale fundus gave a history of 2 days of bilateral blindness 5 months after transplantation and 4 months before this examination. This was associated with

Abbreviations: CMV, Cytomegalovirus; MMF, mycophenolate mofetil

collapse, vomiting, headache and seizures. The patient was on a Tac regime with a level of 11.4 ng/ml (therapeutic range). There was no perception of light and nystagmus on examination with no other ocular or systemic abnormalities. CT scan, lumbar puncture and carotid ultrasound were normal. MRI demonstrated multiple areas of high signal abnormalities in both cerebellar hemispheres and in both parieto-occipital regions. These high signal abnormalities were not present 1 week later. The differential diagnosis was vascular occlusion or tacrolimus related leukoencephalopathy. The visual acuity returned spontaneously after 48 h and at examination the visual acuity was 6/7.5 bilaterally. The patient remained on a Tac regime at the time of this examination.

Another lung recipient had a right phthisis following right endogenous endophthalmitis 2 weeks after transplantation and 8 months before this examination. This was due to *Aspergillus spp.* and although aggressive treatment was systemically successful the eye became phthisical. This patient was an insulin treated diabetic on a MMF regime. She remained on aticonazole and MMF at the time of this examination.

29 patients had repeat ocular examinations with this taking place 1 to 22 months after transplantation (median 3 months). One patient developed a single blot haemorrhage within 1 month of transplantation and another developed early PSCLO between visits but there were no other changes in the ocular findings. 21 of the 29 patients received augmented immunosuppression for rejection episodes.

The ocular findings in relation to their association with transplantation are summarised in tables 1–3.

Of the 115 transplant recipients examined 62 (54%) had findings at ocular examination. The most common findings were cataracts (17% of those examined) followed by hypertensive change (8%), chorioretinal scarring (5%) and diabetic retinopathy (3%). The six patients with chorioretinal changes all had quiescent scars. Five had focal scars, one of which was a peripapillary disciform. One of the patients had bilateral, peripheral, granular scarring inferiorly that would be consistent with previous retinitis but no evidence of active inflammation at the time of involvement in this study. Only one patient was seen to have ocular infective complications following surgery and this was *Aspergillus spp.* endophthalmitis. 18 patients (16%) were symptomatic at examination with the most common symptom being blurred vision. Other reported symptoms were redness, grittiness, stickiness and floaters. 14% of asymptomatic patients had ocular findings that may be associated with transplantation compared to 43% of symptomatic patients. The most common finding in symptomatic patients was cataract

with almost a quarter of patients having posterior subcapsular lens opacity that could be attributed to steroid therapy.

DISCUSSION

This study has the advantage of being prospective. 115 patients received ocular examinations whilst attending the transplant clinic or on the ward so the frequency of screening correlated with the frequency of systemic complications.

It has been advocated that solid-organ transplant recipients require regular ophthalmic screening because the overall visual prognosis is poor in the face of opportunistic ocular infection and early detection improves prognosis.^{5–7} Targeted screening has been suggested as a way to minimise the resources required for maximum return. Porter and colleagues suggested screening the subset of patients in whom vigorous and prolonged rejection phenomenon necessitates the persistent use of immunosuppressive drugs in high doses.⁷ Cho and colleagues suggest screening the subset of patients with post-transplant lymphoproliferative disease as two of their three cases with ocular involvement were asymptomatic.⁸ Erakgun *et al* propose CMV screening in the subset of patients with systemic microvascular risk factors such as diabetes, hypertension and smoking.⁹

Three out of 19 (16%) patients with ocular complications following solid-organ transplantation in Ng *et al*'s retrospective series had CMV retinitis³ whereas only three out of 62 (5%) patients with ocular symptoms in Wapner *et al*'s retrospective cardiac transplantation series had CMV retinitis.¹⁰ In other series of 62¹¹ and 61¹² patients following renal transplantation none of the patients suffered from acute CMV retinitis. Egbert and colleagues at Stanford University reported 11 patients who developed CMV retinitis following heart or kidney transplantation over a 5 year period from 1974.¹³ Their patients had been routinely screened for ocular complications and half were asymptomatic. In a small Turkish study prospective assessment of 13 patients that underwent cardiac transplantation revealed asymptomatic CMV retinitis in two patients (15%).⁹ Despite these very variable results our study suggests that the incidence of CMV retinitis during modern iatrogenic immunosuppression is quite low. This is supported by the fact that a 14 year follow-up of 5721 patients on iatrogenic immunosuppression following haematopoietic stem cell transplantation identified only 10 CMV retinitis cases, one of whom was asymptomatic although asymptomatic individuals were not routinely examined.¹⁴ The asymptomatic patient in this case series was being examined for manifestations of graft-versus-host disease. The variations in incidences of CMV retinitis reported post-transplantation are most likely due to centre effects. Because the ocular complications of transplantation are often associated with organ and life threatening events transplant patients are extremely well monitored for many events. CMV antigenaemia has been shown not to correlate well with ocular disease.¹⁵ Despite this improved surgical technique and immunosuppressive regimes and increasingly effective forms of anti-microbial treatment

Table 1 Ocular findings not associated with transplantation

Ocular findings not associated with transplantation	n
Chorioretinal Scarring	4
Asymmetric disc cupping	2
Flat pigmented choroidal naevi	2
Bilateral maculopathy	3
Bilateral madarosis	1
Blepharitis and medial ectropion	1
Stromal scar in a contact lens wearer	1
Quiet corneal scar following keratitis 12 years previously	1
Hyperope with narrow angles	1
Flat iris naevus	1
Corneal, iris, lens and vitreous changes suggestive of old trauma	1
Congenital Cataract	1
Myopic fundal changes	1
Peripapillary disciform lesion	1
Prominent optic discs and a history of neuroblastoma	1
Homonymous hemianopia which predated transplantation	1

Table 2 Ocular findings probably associated with transplantation

Ocular findings probably associated with transplantation	n
Lens opacities	13
Pseudophakia	4
Extensive chorioretinal scars	1
Large areas of RPE pallor	1
Peripheral perivascular pigment change	1

Table 3 Ocular findings associated with transplantation

Ocular findings associated with transplantation	n
Hypertensive retinopathy	8
Posterior subcapsular lens opacity	6
Mild non-proliferative diabetic retinopathy	4
Horner's syndrome	3
Solitary cotton wool spot	1
Phthisis following <i>Aspergillus</i> spp endophthalmitis	1

and prophylaxis have changed the natural history of opportunistic infection following transplantation.

More surprising, is the low incidence of complications such as diabetic or steroid related cataract, diabetic retinopathy and hypertensive retinopathy in our study. Cataract was the most common ocular complication (17%). Four patients were pseudophakic at examination reflecting prompt access to diagnosis and management of cataract. The low incidence of diabetic and hypertensive retinopathy and the mild signs seen probably reflect the good control and high patient motivation that is required before embarking on transplant surgery.

This study aimed to ascertain the true burden of ocular disease following heart, lung and heart-lung transplantation in asymptomatic as well as symptomatic individuals. It does not support screening of asymptomatic individuals following heart, lung or heart-lung transplantation. Rather, a high index of suspicion is required with prompt and aggressive action when a problem is identified. Patient education must therefore form an important part of any plan to reduce sight-threatening complications. Transplant patients should be encouraged to report promptly if they have ocular symptoms and symptoms should prompt further investigation.

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