The lens after renal transplantation

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Abstract

A single masked observer examined 55 non-diabetic patients chosen randomly from a population of patients who had undergone renal transplant. The mean age was 41 years and mean time from transplant was 4.4 years (1-10 years). Fourteen patients were found to have a posterior subcapsular cataract (PSC). The axial thickness of the right lens of the renal transplant population, even in the presence of a PSC, was significantly larger than in a control population of 99 patients with clear lenses. The PSC of renal transplantation is readily distinguished from age related PSC because the opacity lies in the superficial cortex at a depth proportional to time from transplant and the lens maintains a normal anterior clear zone. It is proposed that this type of cataract be called 'recovering' PSC. It is concluded that the cataractogenic insult occurs mainly during the peritransplant period. Maintenance doses of immunosuppressives or steroids are therefore probably not cataractogenic.

Black *et al* were the first to point out the association of cataract and systemic steroid therapy in their study of patients with rheumatoid arthritis.¹ This association has been recently reviewed by Urban and Cotlier.²

There is good evidence on biochemical^{3,4} and epidemiological⁵⁻⁷ grounds to associate cataract with renal failure. It has been calculated that the relative risk for cataract in renal failure is 12.4.⁷

Several studies have looked at the prevalence of posterior subcapsular cataract (PSC) in renal transplant patients. The reported prevalence pooled from 12 other studies⁸⁻¹⁹ involving 709 patients is 51%. These studies have attempted to relate dose, duration, and total amount of steroid given to the renal transplant patient with the prevalence of PSC, but the results have not been clear cut.

The aim of this study was to characterise clinically the salient features of PSC in renal transplantation (RT-PSC) and to compare them with age related posterior subcapsular cataracts. A further aim was to study the relationship of renal transplant posterior subcapsular cataract to various postulated cataractogenic factors. It has been shown that age related PSC lenses are smaller than normal.²⁰ Therefore our third aim was to study the thickness of the lens of renal transplant patients in order to study the effect of transplantation on lens size.

Materials and methods

Fifty five patients who had undergone renal transplantation between nine months and 10 years previously were studied. All patients were examined by one ophthalmologist (GASS) who

was masked as to the renal status of the patient.

Selection criteria for the renal transplant population were as follows. Patients were excluded if they had had more than one transplant, were aged 56 years or more, were diabetic, or had Alport's syndrome. Patients with congenital or traumatic cataracts were also excluded. The purpose of the upper age limit was to minimise confusion between renal transplant and age related PSC.

PATIENT GROUPING

Patients were grouped according to the different treatment protocols which have evolved over the years. These treatment protocols used at the Renal Unit, Churchill Hospital, Oxford, are summarised as follows:

Group A. Between January 1978 and October 1979 all transplant patients were randomised either to a high dose steroid group (4125 mg of prednisolone over the first 90 days) or low dose steroid group (2544 mg of prednisolone over the first 90 days).²¹ Nine patients from each group were selected at random by means of random number tables for the lens study.

Group B. Between January 1980 and December 1984 all transplant patients were randomised to receive either low dose prednisolone (2175 mg of prednisolone for the first 90 days) and azathioprine or alternatively only cyclosporin for the first three months. After three months all the patients were treated with prednisolone and azathioprine.²² All patients with rejection episodes were treated with boluses of 0.5 g of methylprednisolone. Patients have therefore been further subdivided into those receiving less than 3.0 g and 3.0 g or more of methylprednisolone.

Thus four groups of six patients were chosen by means of random number tables.

Group C. The current regimen for renal transplant patients from January 1985 is known as triple therapy. This consists of cyclosporin 4.0 mg/kg/day, azathioprine 1.5 mg/kg/day, and prednisolone 20 mg/day.²³ A total of 13 patients were chosen at random by random number tables from this group.

As regards the ophthalmic examination of the renal transplant population, all the patients were refracted. Visual acuity was measured by the log MAR Ferris chart.²⁴ Pupils were then dilated with tropicamide 1% drops and phenylephrine 10% drops repeated at least twice in order to produce a pupil diameter of at least 7 mm. The lenses were examined at the slit-lamp and graded by the Oxford clinical cataract classification and grading system.²⁵ The lenses were photographed with the Brown Scheimpflug slit image camera²⁶ and the Oxford retroillumination camera (High Tech Vision).²⁷ Funduscopy was performed. The cup/disc ratio was recorded, intraocular

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pressures were measured by applanation tonometry, and all glaucoma suspects had a Friedmann field examination performed.

SELECTION OF CONTROLS

Staff and relatives of patients, with no known history of significant ocular pathology attending the Oxford Eye Hospital were recruited to the control group. The exclusion criteria included known diabetes, diabetes diagnosed from a random blood test using a reflectance meter, known renal failure, and known ocular pathology such as glaucoma or uveitis. All patients were dilated with tropicamide 1% drops and phenylephrine 10% drops, repeated at least twice until a pupil diameter of at least 7 mm was obtained. Only clear lenses were photographed on the Scheimpflug camera. Our definition of a clear control lens was: no posterior subcapsular cataract, no spoke opacity, normal (grade 3) anterior clear zone, nuclear brunescence (grade 1), and white scatter (grade 1) as defined by the Oxford clinical cataract classification and grading system.²⁵

A total of 99 right eyes were deemed suitable for the study. The age of controls ranged from 13 to 82 years.

AXIAL THICKNESS MEASUREMENTS

The axial thickness of the right lens of the renal transplant population and the controls was measured from the Scheimpflug negatives by image analysis using the Modular Cataract Image Analysis System (Pipistrel PLC) (Sparrow JM, *et al*, unpublished data).

PATIENT DATA

The daily dose of prednisolone, the cumulative dose of methylprednisolone, and the total dose of steroid at one week, one month, and six months after transplantation and at the time of ophthalmic examination was obtained from the notes. The daily dose of azathioprine and cyclosporin A at the same four time intervals was also recorded.

The blood levels of the following electrolytes at those four time intervals were obtained from the notes: glucose, sodium, potassium, urea, creatinine, and calcium. A note was also made of whether the patient had been prescribed any diuretic or calcium antagonist in the preceding period at one week, one month, and six months and at the time of ophthalmic examination.

Results

Fifty five renal transplant patients aged between 21 and 55 were seen. Twelve had bilateral PSC and two had a unilateral PSC affecting the right eye only. One patient was diagnosed as having ocular hypertension. No patient had any field loss detected on the Friedmann field.

ANALYSIS OF RENAL TRANSPLANT SUBGROUP

The effect of possible cataractogenic factors

acting in the peritransplant period was sought. Unpaired *t* tests were performed, and there was no statistically significant ($p > 0.05$) relationship between the daily dose of prednisolone, the cumulative dose of methylprednisolone, and the cumulative dose of steroids and the presence of PSC at the four time intervals defined previously. Similarly there was no demonstrable relationship between the daily dose of azathioprine and cyclosporin A at any of the four time intervals and the presence of PSC in the right eye. We also failed to find any significant association between the levels of electrolytes mentioned previously and PSC ($p > 0.05$).

A χ^2 test was performed on the data for diuretics and calcium antagonists. Here again no statistically significant relationship was found at any of the four time intervals ($p > 0.05$). As regards lens biometry in renal transplant patients and controls: the axial lens thickness of controls was plotted against age. The correlation coefficient was 0.852. The axial lens thickness increased linearly with age and the equation representing the regression line is

$$t = 0.02576 \times A + 3.350,$$

where *t* is the thickness of the lens in millimetres and *A* is the patient's age in years.

This compares with

$$t = 0.0235 \times A + 3.34$$

from Weekers *et al*²⁸ for 150 controls.

Figure 1 is a plot of axial lens thickness of the renal transplant population versus age of patient at time of examination. The interrupted line represents the regression line for controls and the solid line represents the regression line for the renal transplant population. The correlation coefficient is 0.752. The corresponding equation is

$$t = 0.0349 \times A + 3.17$$

It is seen that most data points lie above the dotted line representing the regression line for the control population. Linear regression analysis in groups (analysis of variance) confirms this impression. There is a powerful main effect ($p = 6.26 \times 10^{-6}$) such that lenses of renal transplant patients are on average larger than those of controls after age has been accounted for. There is

Figure 1: Right axial lens thickness (mm) plotted against age of patient (years). Each square represents the right eye of a renal transplant patient. Shaded squares are those with PSC and unshaded squares those without PSC. The interrupted line represents the regression line for the 99 control right eyes, and the uninterrupted line represents the regression line for the 55 right eyes of the renal transplant population.

Figure 2: Thickness discrepancy (mm) plotted against time from transplant (years). Thickness discrepancy = true thickness of lens minus the expected thickness of a control lens matched for age.

Figure 3: Posterior clear zone thickness (mm) plotted against time from transplant (years): $r=0.55$.

in addition an interaction ($p=0.021$) between age and renal transplant status such that the slope of the regression line against age in renal transplant patients is steeper than that of controls.

In Figure 1 the shaded squares represent lenses with PSC and the unshaded squares the clear lenses. The axial thickness of the right lens – with or without cataract – of the renal transplant population is thus significantly larger than a control population.

Figure 2 is a scattergram of the discrepancy in lens thickness of renal transplant patients versus controls plotted against the age of the transplant. Discrepancy = true thickness of the lens minus expected thickness of a control lens corrected for the same age derived from the control regression line.

There was no demonstrable relationship between increase in size of lens and time from transplant. The anterior clear zone of the lens was not reduced in any of the 26 lenses with a posterior subcapsular cataract as judged from standard photographs from the Oxford clinical cataract and grading system.²⁵ All anterior clear zones were graded three (normal).

In nine patients with a PSC it was seen that the PSC did not in fact lie against the posterior capsule but that a zone of optically clear fibres separated the PSC from the posterior capsule. The axial thickness of this zone was measured and plotted against time from transplant in Figure 3. A regression line is drawn. The correlation coefficient is 0.55. The graph shows a tendency for the PSC to lie deeper within the superficial cortex with time. There was no relationship between the grade of PSC and the total amount of steroid given.

In spite of the PSC the reduction in vision was small. The range of recorded LogMAR acuity²⁴ was 0.40 to -0.1 (6/15 to 6/4.5) in those with PSC.

Discussion

MORPHOLOGY OF PSC

The lens grows in thickness throughout life.²⁹ New fibres are continually added to its surface. These fibres are then in turn covered by a newer layer of fibres as further fibres are added. Bio-microscopy of the normal lens shows an anterior clear zone. (ACZ), also known as C1 α , immediately deep to the anterior capsule. This zone is the most recently formed fibres and measures approximately 125 μm in width in vivo; it represents two to three years of growth.

The morphology of the PSC in renal transplantation is interesting. No narrowing of the anterior clear zone (arrowed in Figure 4) was noted even in the patients with PSC seen as early as 21 months and 25 months after surgery. This contrasts with the situation in age related PSC, where the ACZ is consistently reduced or absent.²⁰ The inference is that there is little or no disturbance of new fibre formation and differentiation in the renal transplant patients.

There is a further difference between age related PSC and RT related PSC. A zone of clear fibres can be seen superficial to the PSC in renal transplantation (as shown in Figure 4) but not in age related PSC. This movement inwards of the PSC is analogous to that seen in radiation induced PSC³⁰ and in lamellar cataracts.³¹ Radiation results in a temporary halting of epithelial mitosis, and the re-establishment of mitosis at first results in abnormal fibres in a posterior subcapsular location followed by normal fibres which separate the opacity from the capsule. In

Figure 4: Scheimpflug of a 'recovering' PSC taken nine years after renal transplantation. Note the normal anterior clear zone (arrow) and the PSC which lies away from the posterior capsule (arrow heads).

lamellar cataracts the opacity appears to 'sink' into the lens as new fibres are added superficial to it.

The size of this zone of clear fibres increases with time from transplant, as shown by Figure 3. The low correlation coefficient of $r=0.55$ is probably due to technical difficulties in measuring the size of this zone of clear new fibres: the distances to be measured are small, and it is difficult to decide where the posterior capsule and the PSC lie owing to the amount of forward and backward scatter from the PSC.

It is therefore suggested that in RT PSC, where the ACZ is of normal thickness and the PSC lies deep to a layer of optically clear fibres, the lens has recovered from the cataractogenic stimulus. This concept of a 'recovering' lens implies that the cataractogenic stimulus is no longer acting and therefore that the stimulus was of limited duration acting during the peritransplant period. It is concluded that maintenance doses of immunosuppressives are not cataractogenic. In contrast, in age related PSC, the lens is 'failing': the lens is smaller and the ACZ is reduced or absent.

It is to be noted that the incidence of PSC was relatively low in our group; 12 out of 55 patients (22%) had a PSC in at least one eye compared with 51% from a pooled series of 12 studies.⁸⁻¹⁹ This could in part be due to the fact that in our study patients with Alport's syndrome or diabetes were excluded.

AXIAL LENS THICKNESS

In this study the lens axial thickness in the transplant patients was statistically greater for age than normal lenses whether or not a PSC was present. This is reminiscent of the increased thickness of non-cataractous diabetic lenses reported by Brown *et al.*³¹ and recently for type I diabetics, in whom it has been shown to be related to the duration of diabetes.³²

Steroids have been shown to increase lens cell permeability *in vitro*.³³ It could therefore be hypothesised that increased lens thickness in post-transplant patients is due to an effect on lens permeability. An alternative hypothesis is increased lens growth. Activity of the Na^+ -proton antiport system, which is thought to exist in the lens (Duncan G, personal communication), is coupled in some cell systems to second messenger systems concerned with cell volume regulation and cell growth. The renal hypertrophy which accompanies diabetes mellitus has been attributed to stimulation of the Na^+ -proton antiport system.^{34,35} In x ray cataract the period of mitotic inhibition immediately following exposure is followed by a mitotic spurt above baseline level.³⁶ A similar mechanism could theoretically produce increase lens size in the renal transplant population.

In this study increased lens thickness was noted even in those patients who developed PSC. This is in contrast to age related PSC, where lens size is small for age,²⁰ presumably owing to a reduction in the formation and differentiation of normal lens fibres. The probable explanation for this difference is that there is a limited period in the transplant patients during which cataract is

formed, following which normal fibres are laid down outside the posterior subcapsular opacity.

CONCLUSIONS

It has been shown in the group of patients studied that renal transplantation and its associated therapeutic regimen is associated with the development of PSC in 22%. This PSC is thought to be formed in the peritransplant period. In the groups studied the PSC does not progress, but in time it is followed by the formation of normal clear fibres superficial to the opacity. It is proposed to call this type of PSC a 'recovering' PSC to distinguish it from age related PSC.

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