
CORNEAL GRAFT FAILURE

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PROBLEM:

Blindness is a significant health problem in our country. As per the latest NPCB and WHO survey of 1986-1989 India has about 12 million blind population; which is more than 1/6th of the world and 1/4th of the Asian blindness. After cataract, corneal diseases are the 2nd most frequent cause of blindness and most of such corneal blind patients could be benefited with corneal transplantation. Over one million patients require corneal grafting; 20-25 thousand cases are added annually. Against this heavy demand only 12-13 thousand donor eyes are procured annually. Again of these limited available eyes over 50 % are not suitable either due to inherent poor quality or due to damages incurred during processing.

In India, the first eye bank was established in 1945 at Madras and Dr. Dhanda of Indore carried out the first successful corneal transplantation in 1960. Though there are 171 registered eye banks in the country only 51 are working in the true sense.⁶

PROBLEM MANAGEMENT

With such bleak statistics it is of paramount importance for us in INDIA to identify those patients at risk of graft failure and recognize the symptoms and signs of failure early. Appropriate early and aggressive treatment can make the difference between the success and failure of a graft.

Corneal graft failure may occur as a result of bad donor tissue (primary failure); or due to early or late post-operative complications and in particular due to immunological corneal graft rejection; which is the most common cause of graft failure.

GRAFT REJECTION

A specific process in which a graft, having been clear for at least several weeks (usually longer), suddenly succumbs to graft edema in conjunction with inflammatory signs and this process is immunologically mediated.

IMMUNOLOGY OF GRAFT REJECTION

Corneal graft rejection can occur only in the presence of some degree of histo-incompatibility. The cornea carries major histocompatibility complex (MHC) antigens; the most important being class I (HLA-A and HLA-B) and class II (HLA-DR) antigens. These antigens on a corneal allograft will act as a target structure for immunological destruction of the graft by the host. The foreign anti-

gens are recognized by CD8+ and CD4+ lymphocytes and both delayed hypersensitivity type reaction and direct cytotoxicity are thought to cause target cell destruction.

The concept of direct and indirect allorecognition in graft rejection has been postulated. In the direct pathway, both MHC (Class I) antigens and peptides are of donor origin and are capable of stimulating host T cell directly. In the indirect pathway the foreign antigens are first taken up by the host antigen-presenting cells (Macrophages and Dendritic cells) which process the foreign antigens with their own MHC (Class II) antigens. The resulting complex is then presented to the host T cell for allorecognition.^{3,7}

The general consensus is that corneal graft survival improves with class I matching (Direct pathway) and class II mismatching (Indirect pathway). However the recent Collaborative Corneal Transplantation Study (1992) shows no difference in outcome in high risk patients with and without MHC matching.

COLLABORATIVE CORNEAL TRANSPLANTATION STUDIES (CCTS)-1992

Undertaken at six centres around the USA; enrolled patients were in high risk category. "High Risk" defined as (1) As having more than one quadrant of stromal vascularization and or (2) As having had prior immunological graft failure.

It also defined for the 1st time the graft reaction and its difference from graft rejection

graft reaction : episode of **reversible** immunologic rejection

graft rejection : the end stage of the immunologic reaction that is **no longer reversible**

Patients were screened to determine the presence of preformed antibodies to corneal tissues; and those who had them (less than 10% of the total) were segregated into a CROSS MATCH study to see if the presence of donor antibody increased post-op reaction.

The donor tissue was typed for HLA-A; HLA-B; HLA-DR; and incidentally ABO. An important and perhaps crucial difference in the CCTS study; in contrast to others where there was a positive effect of tissue matching was the clinical management post operatively. Very frequent, high potency topical corticosteroids were used for prolonged periods of time. Stringent criteria for graft reaction (and

rejection) were in place at all centres.

In summary; in 419 eyes where the degree of tissue compatibility was known, and distribution of donor cornea was, in fact designed to achieve zero, one, two or three mismatches; no significant differences in graft rejection (the primary outcome factor) or even graft reaction was found. In addition, having preformed antibodies to the donor tissue did *not* increase rejection, although the number of patients in this group did not permit convincing statistical evidence to this effect.

Surprisingly: ABO compatibility showed a small but detectable enhancement of graft survival.

Conclusion: local or national efforts to obtain the best tissue match do not increase the outcome of high-risk keratoplasty. ABO matching: which can be done at the local eye banks, is feasible, inexpensive and potentially helpful. ^{2,5}

FACTORS AFFECTING GRAFT FAILURE

1. PRE-EXISTING CORNEAL VASCULARIZATION:

Graft rejection is more likely if there is pre-existing corneal vascularization; as this reduces the relative immunoprivilege of the normally avascular cornea.

2. GRAFT SIZE: Large grafts are more likely to reject as they lie near to the limbus and hence nearer to the limbal vessels and host antigen-presenting cells. Small grafts are more prone to failure due to insufficient endothelial cells to maintain function. The **optimal graft size appears to be 7-8 mm**. Graft size greater than 8mm and smaller than 7mm are significantly associated with failure.^{8,9}

3. RECIPIENTS CORNEAL DIAMETER: If greater than 12.5mm horizontally is associated significantly with graft failure.^{8,9}

4. SUTURES: Loose or broken sutures promote local inflammation and vascularization and increase the risks of graft rejection.

5. REPEAT GRAFTS: Repeated grafts have a higher probability of rejection due to **sensitization**. A similar mechanism applies to previous pregnancies and blood transfusion.

6. PRIMARY CORNEAL PATHOLOGY: Rejection is also influenced by the primary pathology of the cornea requiring grafting; e.g.: keratoconus has a very

good prognosis; whilst herpes simplex keratitis has a very poor prognosis.

7. GLAUCOMA MEDICATION: Prolonged glaucoma medication before grafting significantly affects the success of the graft.^{8,9}

Rejection episodes tend to occur soon after surgery; with more than 50% in the 1st 6 months following surgery and 65% of the total rejections in the 1st year. Rejections occurring in the second and third year account for the remaining 20% and 15% respectively. ³

CLINICAL PRESENTATION OF REJECTION

Major symptoms include: ocular irritation, photophobia, blurred vision, and red eye; while major signs include: peri-limbal injection, increased graft thickness (often an early sign), diffuse keratic precipitates, Anterior chamber activity, sub-epithelial infiltrates (resembling adenovirus keratitis), an epithelial rejection line (raised linear aggregates of lymphocytes); and most strikingly an endothelial rejection line popularly called "The Khodadoust Line" (an aggregates of lymphocytes on endothelium arranged in linear fashion); and graft edema.

Both epithelial and endothelial rejection lines start in the periphery at the host-graft junction and move centrally.

MANAGEMENT OF GRAFT REJECTION

The mainstay of treatment of corneal graft rejection is the use of steroids, as lymphocytes are very sensitive to steroids. and also affect many aspects of the inflammatory response itself. Steroids increase levels of adenylyl cyclase and potentiate the effect of beta-adrenergic catecholamines; which diminish the release of vaso-active amines from the mast cells and basophils. These compounds also constrict blood vessels and reduce vascular permeability and post-inflammatory neovascularization. Stabilization of lysosomal membrane occurs. Steroids also induce a transient lymphopenia with the T-lymphocytes more sensitive than B-lymphocytes; thus a suppression of cell-mediated immunity is induced. Phagocytes on the graft endothelium can be destroyed within 24 hours by a topical steroid.⁷

In early phase of rejection: topical steroids are effective. One drop every 10 to 15 minutes or hourly is started. Usually 0.1% dexamethasone drops or 1% prednisolone drops in acetate buffer are used. This regimen may be sufficient to abort an attack and the dose could

be tapered within days to three to four times a day. However if there has been a long interval between the start of the rejection episode and the institution of medication; larger doses may be required, also subconjunctival dexamethasone 4mg may be given every 2nd or 3rd day in addition to hourly topical medication in order to bring the inflammation under control. Some surgeons have resorted to systemic steroids in high risk cases; especially involving one-eyed patients. Doses of over 120 mg prednisolone are administered on alternate days to prevent adrenal suppression. This must be tapered rapidly as soon as clinical response is noted.^{3; 4; 7}

The question often asked is: **how is one to know if the rejection is clearing and how rapidly is the medication to be tapered?** clinical parameters like limbal congestion, graft thickness, graft clarity, graft-host junction and anterior chamber reaction will indicate if there is any improvement. Even after documented improvement, never stop or taper the steroids too rapidly; it has to be graded and gradual. One may know after 2 or 3 days if the graft will clear, since there is usually a dramatic improvement. If however; there is only minimal improvement despite the fact that the K- line appears less regular and the anterior chamber reaction is less, this may indicate that the functioning reserve of the remaining endothelium has been compromised. In such cases it is worth continuing treatment for a number of weeks, although in a reduce dosage. You will be pleasantly surprised at the number of grafts salvaged by not admitting defeat and continuing therapy.

REGRAFTING

But sometimes despite our best efforts the clinical course is downhill and the rejection becomes irreversible. In such cases it is advisable to wait atleast 6 months to a year until the eye is quiet; intraocular pressure controlled and vascularization has subsided before regrafting is planned.

PREVENTION

The patients should be informed of how to recognize the symptoms of graft failure and advised to seek medical attention immediately. One can never overstate the need for meticulous surgery in corneal transplantation, and the need is even greater in high-risk cases. It is a well known fact how faulty alignment

of host and graft can lead to retro corneal membranes, wound leak, peripheral synechiae and iris incarceration which may serve as a nidus for rejection at a later date.

An inflammatory insult can be the inciting factor; be it an ill fitting contact lens causing neovascularization; loose and exposed suture knots, premature suture removal with collapse of the anterior chamber or a recurrence of herpetic infection that is treated only with antiviral medication (not using steroids in combination). Any episodes of suture removal must be covered by an increase in the frequency of administration of topical steroids.^{1,2,3}

If the corneal surgeon takes all these factors into account and always has a high index of suspicion for corneal graft rejection, his/her incidence of this dreaded complication will be reduced.

High-risk cases should ideally be pretreated with steroids. Prefer young donor cornea for transplantation (if you have a choice!) as they have a higher endothelial cell count than older donors as the ultimate failure in rejection is the destruction of the endothelial cells below a **critical reserve**; if the initial cell count is high such donors may be able to survive several attacks of rejection if medication is started early enough.

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...the common eye sees only the outside of things, and judges by that, but the seeing eye pierces through and reads the heart and the soul, finding there capacities which the outside didn't indicate or promise, and which the other kind couldn't detect.

- Personal Recollections of Joan of Arc