Pigmentary Irregularities and Optic Disc Edema After Heart Transplantation

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Objectives: To determine the prevalence of chorioretinal lesions and optic disc edema after heart transplantation and to study potential associations.

Design and Patients: One hundred one patients who had undergone heart transplantation at one institution and 19 patients prior to heart transplantation underwent ophthalmological examination, including fundus photography. The prevalence of fundus lesions was then compared between the two groups.

Main Outcome Measure: With a standardized protocol, the presence of optic disc edema, chorioretinal hypopigmentation and depigmentation, retinal hemorrhages, cotton-wool lesions, and arteriovenous nicking was graded on color transparencies.

Results: The prevalence of optic disc edema and hypopigmentations was significantly higher among the transplant recipients than among the patients prior to heart transplantation (31% vs 5%, P=.01, and 55% vs 11%, P<.001, respectively). Hyperpigmentation was only present in patients after transplantation (15% vs 0%, P=.06). Heart transplant recipients showed an increased risk of hyperpigmentations after 2.5 years. Acute rejection episodes were not associated with posterior pole lesions.

Conclusion: Common posterior pole lesions after heart transplantation are optic disc edema and pigmentary changes. Although visual acuity does not seem severely impaired, further longitudinal study is necessary to evaluate the long-term significance of these lesions.

(Disp Ophthalmol. 1995;113:1281-1285)

ONLY CASE reports have described ocular complications after heart transplantation. Most of them report opportunistic infections and development of ocular tumors, which are both complications of the immunosuppressive regimen after transplantation. Conversely, ocular lesions occurring after renal10 and bone marrow11-16 transplantation have been studied more thoroughly. They may be divided into those involving either the anterior or the posterior segment. Anterior segment complications, such as corneal and conjunctival calcifications and subcapsular cataract, have been well described.17-19 Recent reports have mentioned pathological changes in the posterior segment: chorioretinopathy,17 optic disc edema,18 serous retinal detachment,18 and cotton-wool spots.19 The prevalence and pathogenesis of these lesions, however, remain a matter of speculation.

In this study we aimed to investigate the prevalence of chorioretinal lesions in patients who had undergone heart transplantation, comparing these with a group of patients before transplantation, and to evaluate possible related factors.

RESULTS

Clinical characteristics and demographic data are shown in Table 1. Most heart transplant recipients had hypertension, whereas the waiting list patients were more likely to be hypotensive. The groups were comparable for other clinical features, excluding physical condition and medication. The immunosuppressive medication regimen of cardiac recipients consisted of cyclosporine (100%), prednisone (96%), and azathioprine (23%). Eighty-five patients (84%) were taking antihyperten...
PATIENTS AND METHODS

CARDIAC RECIPIENTS

All cardiac recipients included in this report underwent heart transplantation at the University Hospital of Rotterdam (the Netherlands). Those studied attended the outpatient department of cardiology for a follow-up examination between March and June 1993 (n=115). Of these, 101 (88%) consented; an ongoing rejection episode was the main reason for nonresponse.

PATIENTS PRIOR TO HEART TRANSPLANTATION

The comparison group consisted of patients with end-stage cardiomyopathy who were on the waiting list for heart transplantation. Those eligible were visiting the cardiology clinic or outpatient department during the study period (n=29). To minimize the bias, all patients (66%) participated in the study. Most nonparticipants were in such poor physical condition that ophthalmological examination could not be carried out.

CLINICAL DATA AND DEFINITIONS

From the patients’ records, we obtained information on clinical characteristics about indications for heart transplantation, acute rejection episodes, presence of hypertension, medication, and demographic background. We defined current patient data as those at the time of the ophthalmological examination. Hypertension was defined as a systolic blood pressure of 160 mm Hg or greater and/or a diastolic blood pressure of 95 mm Hg or greater and/or a history of hypertension with use of hypertensive medication at the time of the examination. The definition of a rejection episode was based on histological staging of repeated endomyocardial biopsy specimens according to the guidelines of the International Society for Heart and Lung Transplantation. To minimize patients, all patients were treated prophylactically with a combination of cyclosporine and, in most cases, prednisone. Azathioprine was added to the maintenance immunosuppressive regimen in patients who had had recurrent rejection episodes, in patients who had developed diabetes mellitus (allowing discontinuation of prednisone), and in patients who had developed cyclosporine-related severe renal failure (allowing reduction of the dose of cyclosporine). Rejection episodes were treated with pulsed high doses of methylprednisolone sodium succinate (1 g intravenously on 3 consecutive days) or with polyclonal or monoclonal anti-T-cell antibodies in ongoing or frequently recurring rejection episodes.

OPHTHALMOLOGICAL EVALUATION

Ophthalmological examination consisted of best corrected Snellen visual acuity and, after mydriasis, indirect ophthalmoscopy and fundus photography. Centered on the disc, stereoscopic 20° color photographs were taken, and centered on the macula, stereoscopic 30° color photographs were taken. Retinal angiography was performed in all patients using indocyanine green dye angiography. Fluorescein angiography was performed in cases with optic disc edema and pigmented changes. Visual acuity was not significantly different between the two study groups. In the group after transplantation, 82% had a visual acuity (worse eye) of less than 20/20, compared with 74% of patients before transplantation (P=.3). In each group there was only one patient with a visual acuity (worse eye) of less than 20/20 (1% [1/101] vs 5% [1/19], P=.3).

Prevalence of chorioretinal lesions in at least one eye is shown in Table 2. Optic disc edema, hypopigmentation, and hyperpigmentation were the most common lesions after transplantation, and the prevalence of the first two differed significantly between the two patient groups. Sixty-eight percent (21/31) of posttransplant patients who had optic disc edema had bilateral optic disc edema (Figure 1 and Figure 2). In patients in whom just one eye was involved, only grade 1 optic disc edema was present (Figure 1). Hyperpigmentation was present only in the posttransplant patients. Various patterns of hyperpigmentation were identified: one patient had wide, scattered zones of pigment epithelial disruption and clumping of yellow-orange pigment (Figure 3), three
Table 1. Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Heart Transplant Recipients (n=101)</th>
<th>Waiting List Patients (n=19)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, No. (%)</td>
<td>M 78 (77)</td>
<td>16 (84)</td>
<td>.4</td>
</tr>
<tr>
<td></td>
<td>F 23 (23)</td>
<td>3 (16)</td>
<td></td>
</tr>
<tr>
<td>Mean±SD age, y</td>
<td>48.6±10.7</td>
<td>51.5±8.0</td>
<td></td>
</tr>
<tr>
<td>Age group, No. (%)</td>
<td>15-30 y 6 (6)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>31-40 y 12 (12)</td>
<td>2 (11)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>41-50 y 21 (21)</td>
<td>4 (21)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>51-60 y 44 (44)</td>
<td>11 (58)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥61 y 18 (18)</td>
<td>2 (11)</td>
<td></td>
</tr>
<tr>
<td>Heart disease, No. (%)</td>
<td>Ischemic heart disease 58 (57)</td>
<td>14 (74)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiomyopathy 43 (43)</td>
<td>5 (26)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertension, No. (%)</td>
<td>98 (97)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus, No. (%)</td>
<td>14 (14)</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

Table 2. Fundus Lesions in Heart Transplant Recipients (n=101) and Waiting List Patients (n=19)

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Heart Transplant Recipients, No. (%)</th>
<th>Waiting List Patients, No. (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optic disc edema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>28 (28)</td>
<td>1 (5)</td>
<td>.01</td>
</tr>
<tr>
<td>Grade 2</td>
<td>3 (3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>15 (15)</td>
<td>0 (0)</td>
<td>.06</td>
</tr>
<tr>
<td>Hypopigmentation</td>
<td>56 (55)</td>
<td>2 (11)</td>
<td>.001</td>
</tr>
<tr>
<td>Arteriovenous nicking</td>
<td>22 (22)</td>
<td>1 (5)</td>
<td>.08</td>
</tr>
<tr>
<td>Yellow pigment</td>
<td>6 (6)</td>
<td>0 (0)</td>
<td>.35</td>
</tr>
<tr>
<td>Cotton-wool spots</td>
<td>5 (5)</td>
<td>1 (5)</td>
<td>.55</td>
</tr>
<tr>
<td>Hemorrhages</td>
<td>5 (5)</td>
<td>0 (0)</td>
<td>.42</td>
</tr>
<tr>
<td>Venous branch occlusion</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>.84</td>
</tr>
<tr>
<td>Hard exudates</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>.84</td>
</tr>
</tbody>
</table>

Figure 1. A cardiac recipient with grade 1 optic disc edema; note swollen optic disc with an indistinct margin but maintenance of the physiological cup.

Figure 2. A cardiac recipient with grade 2 optic disc edema; note markedly swollen disc with obliteration of the physiological cup.

patients had a diffuse mottled pattern of pigmentation (Figure 4 and Figure 5), and several patients each had only focal hyperpigmentation or solitary pigmentations surrounded by a halo.

INDOCYANINE GREEN ANGIOGRAPHY

The macular areas of one cardiac recipient showed large zones of disruption and subretinal clumping of yellow-orange pigment. Indocyanine green angiography revealed small areas of nonfluorescence in the choroidal vasculature. These areas corresponded with the subretinal orange deposits (Figure 1).

ASSOCIATIONS WITH AGE, GRAFT REJECTION, AND TIME AFTER TRANSPLANTATION

We evaluated the associations between age, number of acute rejection episodes, time after transplantation, and optic disc edema and hyperpigmentations. Age was not significantly associated with these fundus changes. The number of rejection episodes ranged from zero to 10, with an average of two rejections per recipient. The number of rejection episodes had no significant relationship with optic disc edema or with hyperpigmentations. The mean duration of the posttransplantation period was 3 years, ranging from 1 month to 7.5 years. Patients with a cardiac transplant for more than 2.5 years showed an increased risk of hyperpigmentations compared with patients with a transplant of shorter duration (odds ratio, 10.9; 95% confidence interval, 1.3 to 91.7). There was no association between time after transplantation and optic disc edema. Among patients with optic disc edema, the shortest time after transplantation was 4 months.

COMMENT

Searching the Index Medicus for 1987 through 1995 using the descriptors "heart transplantation" and "ocular complication," we found no report on the prevalence of fundus lesions in a population of cardiac recipients. Hence, we believe this is the first study to address this problem. We detected lesions of the posterior segment in 65 of the 101 patients with a heart transplant. Optic disc edema...
and chorioretinal pigment alterations were the most common of these lesions, and they were significantly more frequent in heart transplant recipients than in a comparable group of patients before transplantation.

Response rates in the posttransplant patient group and the group prior to transplantation were 88% (n=101) and 66% (n=19), respectively. Ongoing rejection was the main reason for nonresponse among posttransplant patients. As the data show, we found no relation between fundus changes and rejection episodes. Frequency of fundus changes is therefore not likely to be different among nonresponding heart transplant recipients. Although exclusion of the most ill patients on the waiting list implies selection, the effect on the results is likely to be small, since all patients on the waiting list were in very poor physical condition prior to transplantation.

There are reports about optic disc edema occurring after other organ transplantations. Gass et al 17 mentioned mild swelling of optic discs in one case after renal transplantation, while others15,16,19 have reported this in groups of patients after bone marrow transplantation. Bernauer et al10 concluded from their cases that the combination of cyclosporine and total body radiation was causing the optic disc edema. Our data show that radiation is not a prerequisite because radiation is not a pretransplantation procedure in cardiac recipients. Avery et al18 ascribed optic disc edema to cyclosporine, arguing that it resolved after discontinuation of this medication. Our patients were taking cyclosporine continuously for life, the oral dose being regularly adjusted according to serum levels. Serum levels of cyclosporine differed only slightly between recipients; therefore, we considered time after transplantation to be a marker for cumulative dose of the immunosuppressive medication. The risk of optic disc edema did not increase with longer time. Thus, if medication is an associated factor, cumulative dose is unlikely to be important.
Hyperpigmentation occurred in 15% of cardiac recipients, hypopigmentation in 35%. Two authors have reported pigmentary irregularities after renal transplantation. Kopsa et al. compared fundus lesions before and after renal transplantation within the same patients, detecting pigmentary changes in 11 of 51 renal transplant recipients. Obermann and Chatterjee described depigmentation in the perimacular area and considered a possible viral cause. Although this cannot be ruled out, postmortem histopathologic examination of one of our heart transplant recipients with pigmentary irregularities showed no signs of infection, only increased fibrosis of the choroidal vessels. This finding is rather nonspecific and can also be detected in hypertensive retinopathy. Cyclosporine could be important in this process, because it is known to cause hypertension and is associated with arteriolopathy.

We identified different patterns of pigmentation. Whether they all have a similar pathological cause is difficult to say. One patient developed severe visual loss associated with zones of disruption and coarse clumping of the pigment epithelium. This lesion closely resembled the posterior chorioretinopathy described by Gass et al. in three patients after renal transplantation and in one patient after heart-lung transplantation. Gass and colleagues commented on an uncertain pathogenesis but hypothesized that localized intravascular coagulation affecting the posterior choroid might be a causative factor. The nonperfused areas of the choroid on the indocyanine green angiogram support this theory. Choroidal vascular occlusion may also be the cause of the focal hyperpigmentation surrounded by a halo. They resemble Elschnig spots, which are ischemic infarcts of the choroid. Whatever causes these pigmentary changes, we found no relationship with acute rejection episodes. The risk did increase with longer time after transplantation, indicating that medication may play a role.

This cross-sectional study was mainly designed to investigate which chorioretinal lesions occur after heart transplantation; therefore, our ability to draw valid conclusions on possible causes is limited. Only prospective follow-up studies will provide more clues about time of onset, natural course, and etiology. We conclude that marked fundus changes are not as frequent as previous case reports suggest. Nevertheless, optic disc edema and pigmentary irregularities are common after heart transplantation. As the life expectancy of cardiac recipients increases, a study of the long-term ophthalmological effects of heart transplantation and the consequences of the immunosuppressive regimen may become indicated.

Accepted for publication May 26, 1995.

The authors thank cardiologist Agnes Balk, MD, PhD, for enabling data collection, and statistician Paul Mulder, PhD, and Stephan Locke, MD, PhD, for their review and constructive criticism of the article.

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