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Fifteen years' experience with renal transplantation in systemic amyloidosis

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Abstract. At our center 62 renal transplantations (31 living donor and 31 cadaveric donor grafts) have been performed in 58 patients with amyloid renal disease since 1974. The amyloidosis was secondary to rheumatic disease in 74% of the patients. Predialytic transplantation was performed in 28% of the patients. Mean follow-up time was 5.1 years (0.3–14.5 years). One-year actuarial patient survival was 79%, decreasing to 65% after 5 years. First graft survival was 74% at 1 year and 62% at 5 years. Patient death with a functioning graft caused 16 out of 25 graft losses. Infections caused 11 out of 18 deaths (61%), more than half of them within 3 months. Renal transplant amyloid was diagnosed in about 10% of the cases (6/62); however, only about 3% of the grafts (2/62) were lost. These long-term results encourage transplantation in amyloid renal end-stage disease.

Key words: Amyloidosis, kidney transplantation – Kidney transplantation, systemic amyloidosis

Renal involvement in systemic amyloidosis is common and renal failure is a major cause of death in patients suffering from it [5, 6, 15, 21]. Most cases are caused by rheumatic diseases, especially rheumatoid arthritis [2, 5, 7, 9]. Decades of active illness often precede amyloid renal failure, at which time other organs are often affected [6, 8]. For this reason renal transplantation has not been an option for these patients.

The first case report of a successful renal transplantation in amyloid renal end-stage disease was given by Belzer and coworkers in 1968 [3]. For more than a decade, the experience was limited to a small number of patients [1, 9, 11–13]. The clinical outcome after renal transplantation therefore remained uncertain until 1986, when Pasternack et al. [17] published results from transplantation in 45 patients. The graft survival rates were satisfactory, although not as good as for matched controls (glomerulonephritic patients). Before 1986 renal transplantation was not generally accepted as the treatment of choice in amyloid renal failure. By 1983, our preliminary experience with 21 renal transplantations in amyloid renal failure was that about two-thirds of the patients survived 4 years. Given this background a more aggressive transplant program was started with amyloid patients. We now present long-term, follow-up results of 62 renal transplantations in amyloid renal end-stage disease from one center.

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Materials and methods

All transplantations in Norway are performed at our center, which serves 4 million inhabitants. During a 15-year period starting November 1974, 58 patients (27 men and 31 women) received 62 renal transplants due to amyloidosis with renal failure. More than half of the patients were transplanted during the last 4 years, comprising about 5% of all transplantations performed during this period. The average observation time after transplantation was 5.1 years (range 0.3–14.5 years). No patient was lost to follow-up. The mean age at transplantation was 46.2 years (range 18–69 years).

Amyloid renal failure complicated rheumatic disease in 43 patients (74%); 30 of these patients suffered from rheumatoid arthritis (RA), 7 from psoriatic arthropathy, and 6 from ankylosing spondylarthritis (AS). Seven patients (12%) suffered from Crohn's disease, which, in two cases. was combined with RA or AS. Renal amyloid complicated the primary disease after 20 ± 9 years, estimated at the time of transplantation. Eight patients (14%) had no signs of other chronic disease and were considered to have AL (light-chain, primary) amyloidosis.

Amyloid data

In 44 patients (76%) the diagnosis was confirmed by biopsy of the kidney or other organs. In 14 patients the diagnosis was based on clinical criteria; in 1 of these the diagnosis was verified at autopsy. Amyloid was diagnosed by examination of kidney, liver, or mucosal biopsies in polarized light after straining with alkaline Kongo red dye and, in some cases, by electron-microscopical examination. No histochemical differentiation between AA (secondary) and AL (primary) forms was performed.

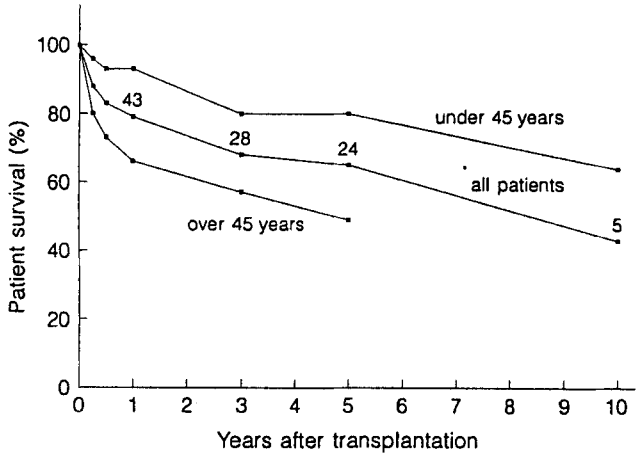

Fig. 1. The *middle curve* shows the overall actuarial patients survival, the *upper and lower curves* the survival of patients aged under and over 45 years, respectively. The numbers on the curve refer to the number of patients left to observation at 1, 3, 5, and 10 years

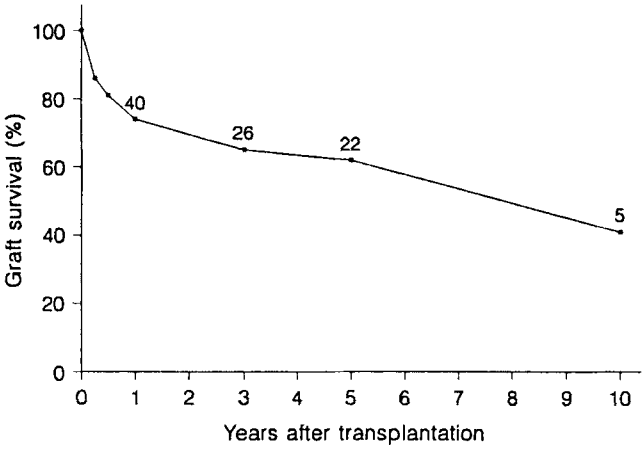

Fig. 2. Actuarial graft survival is shown. The numbers on the curve refer to the number of grafts left to observation at 1, 3, 5, and 10 years

Hemodialysis was started in 42 patients on the average 9.6 months (range 1–32 months) before transplantation; 16 were transplanted predialytically.

The donor was living related in 29 patients. Eight were HLA-identical; 18 were mismatched for one and 3 were mismatched for both HLA haplotypes. Two patients received a graft from a spouse, and 31 grafts were provided by cadaveric donors. Second grafts ($n = 3$) and third grafts ($n = 1$) were cadaveric transplants.

Immunosuppressive therapy consisted of high-dose prednisolone and azathioprine until 1983. Later, cyclosporin was used in combination with low-dose prednisolone and, in most cases, azathioprine. Rejection episodes were treated with repeated boluses of methylprednisolone and/or antilymphocyte globulin (ATG, Fresenius) when necessary.

Statistics

Actuarial survival was calculated using the standard life table method. Differences between survival curves for different subgroups were tested with the Mantel-Haenszel log rank test (chi-squared statistics).

Results

Figure 1 shows the actuarial patient survival for the whole group of patients up to 10 years after transplantation. Separate survival curves for patients below and over 45 years of age are also shown. Overall early mortality was high; the survival rate was 95% at 1 month, 88% at 3 months, and 79% at 1 year. Patient survival was 65% at 5 years and 43% at 10 years. The survival curve is significantly better for the group of patients below 45 years of age than over 45 ($P < 0.01$). The 1-year survival rates were 93% and 66%, respectively. The dialytic status at transplantation had no significant impact on mortality. Three of the 16 patients transplanted before dialysis was started (19%) died during the 1st year compared to 9 out of 42 patients (21%) treated with dialysis before transplantation.

No differences in patient survival were observed with regard to the primary disease. Also, patients with primary or AL amyloidosis did as well as those with the secondary or AA form. A comparison between the biopsy-verified patients and those with a clinical diagnosis only revealed no differences. Living donor recipients suffered 7 deaths compared to 11 in the group receiving cadaveric grafts. This difference was, however, not statistically significant ($P < 0.19$). Although cyclosporin-treated patients showed a tendency towards better survival, statistical significance was not reached ($P < 0.23$). Table 1 shows the causes of death in 18 patients. Infections (pneumonia and/or septicemia) accounted for 61% of all deaths and 75% of the deaths occurring during the 1st year. Cardiovascular complications caused 17% of all deaths. Heart involvement with amyloid was not suspected in any of the cases, nor could any death be ascribed to liver failure due to amyloid disease.

The actuarial first graft survival rates are shown in Fig. 2 and are largely influenced by the fact that 16 out of 25 graft losses were due to patient death with a functioning graft. The graft survival was 95% at 1 month, 86% at 3 months, 81% at 6 months, 74% at 1 year, 62% at 5 years, and 41% at 10 years. Table 2 gives the causes of

Table 1. Causes of death

	Months after transplantation		
	0–3	3–12	> 12
Pneumonia/septicemia	6	3	2
Cardiovascular complications	2	0	1
GI bleeding/pancreatitis	0	1	1
Unknown	0	0	2
Total	8	4	6

Table. 2. Causes of graft losses

	Years after transplantation			
	0–1	1–2	2–5	> 5
Patient death	11	3	1	1
Amyloid	0	0	1	1
Rejection	4	1	0	0
Unknown	0	0	0	2
Total	15	4	2	4

graft loss and their relation to time after transplantation. Four grafts were lost during the 1st year and another graft after 2 years, due to rejection. Two patients lost their grafts due to recurrent amyloid 3.5 and 7 years after transplantation, comprising 3 % of all transplants and 8 % of all graft losses. Recurrence of renal amyloidosis was diagnosed in six patients (10 %), but in four of these with sustained renal function. The earliest case of recurrent amyloid was found at autopsy 1.5 years after transplantation in a graft that functioned well until death. Finally, two grafts were lost more than 5 years after transplantation for unknown reasons. Four retransplantations were performed in three patients. Two patients received a second graft 2 and 8 years after their first transplant. One patient also received a third graft more than 8 years after the first one. Two of these patients were alive with functioning grafts at follow-up.

Finally, graft survival showed a tendency to improve with cyclosporin treatment; however, this was not statistically significant ($P < 0.23$).

Discussion

The long-term survival rates described here – with almost two-thirds of the patients alive after 5 years – support the use of renal transplantation as a major mode of therapy in amyloid renal end-stage disease. However, we did observe a high early mortality rate in our patients as a result of infection. These results are in agreement with previous findings reported by Pasternack et al. [17] and Isoniemi and associates [10], but the observation time is longer and the number of patients higher in our study. The high incidence of early and lethal infections is most striking and demands attention in order to improve the survival rates in these patients. Both early diagnosis and effective treatment of infections are warranted. These patients may well be immunodeficient as a result of their primary disease, but first of all due to amyloidosis.

It is well known from autopsy studies that the spleen is commonly involved with amyloid disease [8]. Scintigraphic evaluation of patients with systemic amyloidosis in vivo has recently been published demonstrating that in most cases of both AA and AL amyloidosis, the spleen is severely affected [8, 18]. The changes are destructive and impair organ function [7] and may, therefore, be associated with a higher incidence of septicemia, as with surgical splenectomy [20]. A recently published survey of renal transplantation in infants also focused on the importance of conservation of the spleen to avoid late septicemia [16]. Amyloidosis of the spleen might therefore contribute to the high incidence of septicemia in these patients. In addition, bone marrow may be compromised with AA amyloid and the liver with both forms of amyloid [6, 8] with increased risk for infections.

Most of the patients in our study had received long-term immunosuppressive therapy before transplantation. Nevertheless, all of our patients were given standard renal transplant immunosuppressive and rejection therapy. All of the patients who died from septicemia had received rejection therapy, either with methylprednisolone alone or in combination with ATG. On the other hand, a reduced number of rejection episodes would be expected if patients with amyloidosis were significantly more immunodeficient than other renal transplant recipients. In accordance with this, a tendency towards fewer rejection episodes in amyloid patients has been noted by others [17, 19]. Such a tendency, however, was not found in our patients.

It came as no surprise that the number of deaths increased significantly with age. The fact that 10 out of 12 patient deaths in the 1st year occurred in the older group (> 45 years) indicates that resistance against infection is inferior in this group. The possibility of overimmunosuppression should be kept in mind with transplantation in systemic amyloidosis. This may be especially important during the first 3 months, during rejection episodes, and in older recipients, factors correlated to infection and mortality.

The survival of both patient and graft may be influenced by the nature of the primary disease. We found no differences between patients with rheumatic disease and patients in other groups. Patients with the clinical diagnosis of amyloidosis had the same patient and graft survival as biopsy-verified cases. The prognosis with AA amyloidosis was not significantly different from that of the AL form. Systemic deposition of amyloidosis will, by nature, proceed progressively [18]. One might speculate that the immunosuppressive regimen given after transplantation would retard progression of the disease. On the other hand, it was soon recognized that amyloidosis may also involve the transplanted kidney [4]. Fewer than 10 % of our patients suffered from graft amyloidosis. This was less than previously estimated [17], and only one-third of the cases led to graft loss. However, experience with amyloid native kidney disease would lead one to expect more grafts to be lost with time [6, 21]. Also, the true incidence of graft amyloidosis remains uncertain since biopsies were only performed when unexplained proteinuria or a rise in creatinine was observed. Nevertheless, amyloid recurrence had little impact on long-term graft survival in our study and, from a practical point of view, was no serious problem. It has been shown that cytotoxic anti-inflammatory treatment of patients with rheumatoid arthritis complicated with type AA amyloidosis can improve their prognosis [2]. Although nephrotic syndrome caused by the AL form of amyloidosis may be reversed by such therapy, the renal amyloid deposition increased despite therapy [14], and the prognosis is considered poorer with AL than with AA disease [5]. However, all cases of graft amyloid in our study were diagnosed in AA patients. Renal transplantation may, therefore, be performed in both forms of amyloidosis.

Treatment with cyclosporin did not significantly improve patient or graft survival in our study. This may be explained by the relatively low number of patients in the two groups. Isoniemi et al. found an increased graft survival with cyclosporin treatment in amyloidosis [10]. Although cyclosporin is superior to azathioprine in suppressing rejection episodes, there is also an increased risk of infection with cyclosporin treatment. On the other hand, the doses of prednisolone were higher before cy-

closporin treatment was introduced and might have rendered the patients as susceptible to infections as with cyclosporin.

Despite a high early mortality from infections and some recurrence of graft amyloid disease in our patients, the 5-year overall survival rate was 65%, which does not differ much from that for renal recipients in general at our center. One alternative could be to treat the patients with chronic dialysis, but experience elsewhere with chronic hemodialysis of patients with amyloidosis has not been too encouraging [5, 9, 11, 15]. Another alternative could be CAPD [5, 17, 18], but long-term results are lacking, and given these patients' susceptibility to infection, CAPD may be hazardous.

We therefore conclude that renal transplantation may be the best treatment for systemic amyloidosis with renal failure.

References

1. Advisory Committee to the Renal Transplant Registry (1975) Renal transplantation in congenital and metabolic disorders. A report from the ASC/NIH Renal Transplant Registry. JAMA 252: 148–153
2. Ahlmen M, Ahlmen J, Svalander C, Bucht H (1987) Cytotoxic drug treatment of reactive amyloidosis in rheumatoid arthritis with special reference to renal insufficiency. Clin Rheumatol 6: 27–38
3. Belzer F, Ashby B, Gulyassy P, Powell M (1968) Successful seventeen-hour preservation and transplantation of human-cadaver kidney. N Engl J Med 278: 608–610
4. Benson MD, Skinner M, Cohen AS (1977) Amyloid deposition in a renal transplant in familial Mediterranean fever. Ann Int Med 87: 31–34
5. Browning M, Banks R, Tribe C, Bacon P, Hollingsworth P, Kingswood C, Poulding J, Harrison P, Mackenzie C (1983) Renal involvement in systemic amyloidosis. Proc EDTA 20: 595–600
6. Cohen AS (1967) Amyloidosis. N Engl J Med 277: 628–638
7. Glenner GG (1980) Amyloid deposits and amyloidosis. The beta-fibrilloses II. N Engl J Med 302: 1333–1343
8. Hawkins PN, Lavender JP, Pepys MB (1990) Evaluation of systemic amyloidosis by scintigraphy with ^{123}I-labelled serum amyloid P component. N Engl J Med 323: 508–513
9. Heering P, Kutkuhn B, Frenzel H, Linke RP, Grabensee B (1979) Renal transplantation in amyloid nephropathy. Int Urol Nephrol 21: 339–347
10. Isoniemi H, Eklund B, Höckerstedt K, Salmela K, Ahonen J (1989) Renal transplantation in amyloidosis. Transplant Proc 21: 2039–2040
11. Jones NF (1976) Renal amyloidosis. Pathogenesis and therapy. Clin Nephrol 6: 459–464
12. Kennedy CL, Castro JE (1977) Transplantation for renal amyloidosis. Transplantation 24: 382–385
13. Kuhlbäck B, Falck H, Törnroth T, Wallenius M, Lindström BL, Pasternack A (1979) Renal transplantation in amyloidosis. Acta Med Scand 205: 169–172
14. Kyle RA, Wagoner RD, Holley KE (1982) Primary systemic amyloidosis. Resolution of the nephrotic syndrome with melphalan and prednisone. Arch Intern Med 142: 1445–1447
15. Leading article (1980) Treatment of renal amyloidosis. Lancet I: 1062–1063
16. Najarian JS, Frey DJ, Matas AJ, Gillingham KJ, So SSK, Cook M, Chavers B, Mauer SM, Nevins TE (1990) Renal transplantations in infants. Ann Surg 212: 353–365
17. Pasternack A, Ahonen J, Kulbäck B (1986) Renal transplantation in 45 patients with amyloidosis. Transplantation 6: 598–601
18. Pepys MB (1988) Amyloidosis: some recent developments. Q J Med 67: 283–298
19. Pras M, Gafni J, Jacob ET, Cabili S, Zemer D, Sohar E (1984) Recent advances in familial Mediterranean fever. Adv Nephrol 13: 261–270
20. Styrt B (1990) Infection associated with asplenia: risks, mechanisms and prevention. Am J Med 88: 33N–42N
21. Törnroth T, Falck HM, Wegelius O (1985) Renal pathology in amyloidosis. Scand J Urol Nephrol [Suppl] 90: 9–21