Response of patients with renal involvement by progressive systemic sclerosis to antihypertensive therapy


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Summary

1. Renal involvement in progressive systemic sclerosis is characterized by hypertension, grade III or IV hypertensive retinopathy, rapidly progressive renal failure and enhanced plasma renin activity.

2. Of 70 patients with progressive systemic sclerosis involving the kidneys seen since 1955, 48 died within less than 3 months and 16 are alive or survived longer than 1 year.

3. Aggressive antihypertensive therapy was the principal factor that prevented early death in the 16 survivors.

4. Angiotensin converting enzyme inhibition with captopril appears to be the treatment of choice at present, but methyldopa or minoxidil may be successful in certain patients whose response to captopril is not satisfactory.

Key words: antihypertensive therapy, captopril, kidney, systemic sclerosis.

Abbreviations: PRA, plasma renin activity; R-PSS, renal involvement by progressive systemic sclerosis.

Introduction

Ten years ago, Medsger et al. reviewed 309 cases of progressive systemic sclerosis (R-PSS) and showed that acute renal involvement by this disease carried an ominous prognosis, with survival that never exceeded 6 months [1]. The experience of others was similar [2, 3]. During the past decade, however, a number of case reports have appeared in the literature, showing a better outcome in some patients with R-PSS [4–9].

Most of these patients with a prolonged survival were treated by chronic dialysis with or without nephrectomy [3–5], a few received kidney transplants [3–5] and a small minority was reported to have been saved by vigorous antihypertensive therapy [5–9]. Our results at the University Health Center in Pittsburgh similarly have been more encouraging in recent years. In this article we present data regarding our series of 70 R-PSS patients treated over the last 25 years and the impact of some of the newer drugs and methods of management on survival.

Methods

The charts and special records of all the patients with a clinical diagnosis of R-PSS, who were admitted to and followed at the University Health Center in Pittsburgh since 1955, were reviewed. The clinical diagnosis of R-PSS was ascertained in the light of more recent literature [3, 10]. The following information was sought in each record: date of admission, age, sex, years of progressive systemic sclerosis before the onset of R-PSS, pertinent findings on physical examination including blood pressure measurements and eye-ground examinations, information documenting visceral involvement other than renal, laboratory values including serum creatinine and/or blood urea nitrogen and plasma renin activity (PRA). The reports on microscopical evaluation of kidney tissue were carefully reviewed wherever available. Compatibility with a histological diagnosis of R-PSS was based on generally accepted criteria [3, 10, 11]. PRA was measured by bioassay [12] before 1971 and by radioimmunoassay [13] since 1971.

Results

Seventy patients (45 women and 25 men) were admitted to the University Health Center in
FIG. 1. Number of patients admitted for R-PSS by season of year.

Pittsburgh between 1955 and 1981 because of R-PSS. Twenty-nine were treated before 1970 and the remaining 41 since 1970. The diagnosis of R-PSS was based on clinical criteria in all but two cases, in whom it was established post mortem. Autopsy, nephrectomy or renal biopsy specimens were obtained from 40 clinically diagnosed R-PSS patients and in all these cases, without exception, the histological picture was consistent with the diagnosis of R-PSS. The most consistent clinical findings (besides the characteristic skin changes of scleroderma that were present in all the patients) were the following: (a) diastolic hypertension, which was present in 90-99% of 66 cases (in four early cases the blood pressure charts could not be retrieved); (b) grade III or IV Keith–Wagener hypertensive retinopathy, which was present in 88% \( (n = 59) \); (c) a serum creatinine greater than 130 \( \mu \)mol/l and/or blood urea nitrogen greater than 10.0 mmol/l, which was found in 68-7% at the time of admission and eventually reached these values in 93-7% of the patients \( (n = 67) \); (d) a raised PRA which was determined in a total of 41 patients (five by bioassay, 34 by radioimmunoassay and two by both methods). In 92-7% of these patients it was greater than twice the upper limit of normal at the time of admission and eventually became elevated to this level or above in 97-6%. In 41.5% of the patients PRA was greater than 10 times the upper limit of normal, in some cases reaching values up to 100 times normal. The average PRA for the 41 patients at the time of admission was 12 times the upper limit of normal. PRA was found to be less than twice the upper limit of normal in all 11 cases in which it was measured, shortly (1 week to 1 year) before the onset of R-PSS, but rose to much higher levels as soon as R-PSS was noted.

In 22 (or 55%) of the 40 subjects in whom data are available for the above four characteristics, all four were 'positive' and in another 17 (43%) three of the four were 'positive'. Thus on admission, 98% of the subjects had at least three of the four characteristics. Of 19 patients for whom we have data on only three of the above characteristics, eight (42%) were 'positive' for all three and nine (47%) for two of the three. Of the patients with R-PSS 71% exhibited other visceral (as well as renal) involvement and 32% of these had myocardial involvement by progressive systemic sclerosis.

Additional observations included rapidly progressive skin thickening preceding the onset of R-PSS [14] and a significant tendency for our patients to develop R-PSS during the fall and winter months (Fig. 1).

The average age at onset of R-PSS was 51.2 (range 22–74) years and the average time which had elapsed after the diagnosis of progressive systemic sclerosis had been made, was 3.0 (range 0–12) years. Mean survival for the 29 patients seen between 1955 and 1969 was 31 days and none lived longer than 100 days. Another 25 patients, who were seen between 1970 and 1980, lived 64 days on the average, with six of them surviving between 3 and 7 months. The length of survival was thus rather short in all these 54 patients and we can consider them as one group.

Since 1970 we have also managed 12 patients who lived longer than 1 year (average 4.2 years, range 1.5–10.5 years) and eight of these are still alive (average 4.4 years). In addition, four patients who have been treated within the last year are alive and have to date shown no further progression of renal failure. This group of 16 patients was somewhat younger (average 47.8 years), but there was considerable overlap in the age ranges of the two groups. Seven of the 16 (44%) were 'positive' for all four of the typical clinical characteristics of R-PSS described above and the remaining nine were 'positive' for three of these. Visceral involvement other than renal was present in 69% and, of these, 45% had myo-
cardial involvement. The treatment of these 16 patients consisted primarily of the following: methyldopa (or propranolol) ± hydralazine, four patients; methyldopa (or propranolol) ± hydralazine + chronic dialysis, four patients; minoxidil + propranolol, one patient; minoxidil + propranolol + dialysis, three patients; captopril, four patients. Four of the seven chronically dialysed subjects subsequently underwent bilateral nephrectomy because of persistent uncontrollable hypertension. The nine surviving patients who were able to avoid dialysis included the four successfully treated with captopril, one treated with minoxidil, and four whose renal impairment was only slowly progressive and responded to combinations of methyldopa, propranolol and hydralazine.

Among the patients who were treated with the above forms of therapy other than captopril, 24 died early (i.e. after less than 1 year, average 69.4 days). These included 11 who were dialysed, of whom three had bilateral nephrectomy. Their renal function deteriorated rapidly, with blood urea nitrogen rising from 18.5 ± SD 13.8 mmol/l on admission to 53.6 ± 20.9 mmol/l shortly before death, in contrast to the 16 survivors whose renal function remained relatively stable (blood urea nitrogen = 20.3 ± 14.1 mmol/l on admission and 26.1 ± 14.4 mmol/l when last assessed). The four patients who were treated with captopril and had a satisfactory response stabilized or even improved their renal function (initial and final mean serum creatinine 302 and 239 μmol/l respectively). The serum creatinine of one of these patients rose in one week from 355 to 770 μmol/l despite good control of blood pressure with minoxidil, but he has now received captopril for over 2 years and his serum creatinine has been stable at 500–550 μmol/l.

In contrast, two additional patients who received captopril were treatment failures. One had a paradoxical hypertensive response and developed hypertensive encephalopathy on the third day of treatment with captopril, despite the typical changes in PRA and angiotensin converting enzyme. She was subsequently treated with minoxidil and haemodialysis and 8 months later we were able to discontinue dialysis; 20 months later, her blood pressure remains under good control and her serum creatinine is 270 μmol/l. Finally, the other captopril failure is the only R-PSS patient in our series who did not have a marked elevation of PRA. His blood pressure was eventually brought under good control with methyldopa and the deterioration of kidney failure was arrested.

Discussion

The syndrome of R-PSS is characterized by the sudden onset of a clinical tetrad consisting of hypertension, accelerated or malignant hypertensive retinopathy, rapid deterioration of renal function and enhanced PRA. The sequence of the appearance of these four clinical findings is variable, but the development of any one of them usually heralds the prompt occurrence of the other three with enhanced PRA as an almost invariably finding. On the other hand, we did not find a marked elevation of PRA before the development of R-PSS, although others have claimed that such an elevation may precede imminent renal impairment [15]. It is of interest that in the Western Pennsylvania area, the onset of the cold months seems to bring with it an increased incidence of R-PSS, suggesting perhaps environmental (i.e. temperature) or other extrinsic precipitating causes for the suddenly enhanced renal vasoconstriction.

Whether or not the renin–angiotensin system is a primary factor in the rapidly fatal course of R-PSS, its suppression by bilateral nephrectomy has occasionally resulted in good control of blood pressure and prolonged survival of the patients. On the other hand, effective blood pressure control by dialysis, even without nephrectomy, or by potent pharmacological agents such as minoxidil, which do not inhibit the renin–angiotensin system, have also been found occasionally to be beneficial by us, as well as by others [5, 6]. However, the most impressive effects which we have obtained have been those due to inhibition of angiotensin converting enzyme by captopril.

Beneficial results with this drug in our hands are in accord with those reported by others [9, 16]. In our experience, measurement of the decline in angiotensin converting enzyme activity has been helpful in following the patients treated with captopril. Failure of its decline may represent either the patient’s non-compliance with therapy or an insufficient dose.

Currently we recommend the following therapeutic approach in R-PSS: if renal function is not deteriorating very rapidly and PRA is not markedly enhanced (not over 10 times normal), the antihypertensive regimen should consist of a diuretic + propranolol (or methyldopa) ± hydralazine. If this fails to control the blood pressure or if renal function subsequently deteriorates, captopril is substituted. If PRA is elevated 10 times normal or above, and/or renal function deteriorates rapidly, captopril is the drug of choice at present, with the occasional addition of β-adrenoceptor blockade. If this fails, minoxidil ± dialysis ± nephrectomy can be considered.
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References