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Chinese herbs nephropathy presentation, natural history and fate after transplantation

F. Reginster, M. Jadoul and C. van Ypersele de Strihou

University of Louvain Medical School, Cliniques Universitaires St-Luc, Department of Nephrology, Bruxelles, Belgium

Abstract

Background. Chinese herbs nephropathy is a new type of subacute interstitial nephropathy reported in women who had followed a slimming regimen including Chinese herbs.

Methods. We report the clinical presentation and follow-up of 15 cases and compare them with a control group of 15 women with interstitial nephropathies of other origins, matched for age, sex, and initial serum creatinine (mean 3 mg/dl).

Results. At presentation the Chinese herbs nephropathy group differed from the control group by a lower proteinuria ($P=0.009$), a more severe anaemia ($P=0.002$), and a higher prevalence of aortic insufficiency (42% vs 0%, $P<0.05$). It was further characterized by mild hypertension in 80%, glycosuria and leukocyturia in 40% and asymmetric kidneys in 54% of the cases.

During follow-up, deterioration of renal function was faster in the Chinese herbs nephropathy than in the control group ($P<0.05$). It was influenced by the duration of Chinese herbs treatment ($P=0.037$) and the delay between the end of Chinese herbs ingestion and diagnosis of the disease ($P=0.013$). In three cases, renal failure developed 3 years after Chinese herbs ingestion. Complications included severe aortic regurgitation requiring surgery ($n=1$), urothelial carcinoma ($n=2$), bilateral ureterohydronephrosis due to periureteral fibrosis ($n=1$).

Five patients with Chinese herbs nephropathy were successfully transplanted, without evidence of recurrence of the disease.

Conclusions. Chinese herbs nephropathy is characterized by a lower proteinuria, more severe anaemia, and a faster progression to renal failure than other interstitial nephropathies. The duration of Chinese herbs treatment and interval between withdrawal of Chinese herbs and diagnosis are correlated with the rate of progression. Severe, unusual extrarenal complications may affect Chinese herbs nephropathy patients.

Correspondence and offprint requests to: C. van Ypersele MD, Cliniques Universitaires St-Luc, Department of Nephrology, av. Hippocrate 10, 1200 Bruxelles, Belgium.

Key words: aristolochic acid; Chinese herbs; Chinese herbs nephropathy; interstitial nephropathy

Introduction

A new type of rapidly progressive interstitial fibrosis of the kidneys has been recently reported in Belgian women who had followed the same slimming regimen including Chinese herbs, the so-called Chinese herbs nephropathy (CHN) [1]. Several characteristics of this nephropathy have been highlighted: development of end-stage renal disease (ESRD) within 1–2 years [1], histology showing a striking extensive interstitial fibrosis [2,3], urothelial atypias and malignancy [2,4,5] and low-molecular-weight proteinuria [6].

The unique characteristics of this disease warrant a comprehensive description of its presentation and evolution. We report 15 cases followed at our hospital between October 1991 and June 1995. Their clinical and biochemical characteristics at presentation, as well as the progression of renal failure are compared with a similar group of 15 patients followed, in our department, for chronic interstitial nephritis of other origins (control group). Complications of the disease and fate after transplantation are described.

Subjects and methods

This retrospective analysis was carried out in patients who had attended the X Clinic and taken the formula 2 slimming cure [1] for 2–24 months between May 1990 and July 1992 and who had been referred to our department between October 1991 and June 1994. Formula 2 included Stephania tetrandra, Magnolia officinalis, fenfluramine, diethylpropion, cascara powder, acetazolamide, belladonna extract, meprobamate (all of them orally), and injections of artichoke extract. All 15 patients with evidence of renal failure (serum creatinine >1.3 mg/dl) were included.

The duration of the slimming regimen was taken as the number of months during which formula 2 pills were ingested.

The delay between the end of the slimming regimen and the diagnosis of Chinese herbs nephropathy was calculated (free interval).

All patients underwent a physical examination and standard blood and urine tests. Kidney size was evaluated by plain abdomen X-ray with kidney tomography in 13 patients. A standard echocardiography was performed in 13 patients. The patients were followed at the out-patient clinic approximately every 3 months. Follow-up extended to 30 June 1995 (range 12–43 months).

The clinical pattern and the evolution of renal function of the Chinese herbs nephropathy group were compared with those of a control group of 15 women with various other interstitial nephropathies, matched for age and initial serum creatinine. Their diagnoses were: analgesic nephropathy ($n=1$), chronic pyelonephritis ($n=9$, 3 with reflux nephropathy), and chronic interstitial nephropathy of unknown origin ($n=5$) which was identified on clinical grounds including, in all five cases, mild hypertension, leukocyturia, glycosuria, tubular acidosis, and low-grade proteinuria as well as a marked, often asymmetric shrinking of the kidneys on imaging procedures, and on the basis of a biopsy in one case.

All control patients underwent echocardiography.

Statistical analysis

The time required for doubling of serum creatinine (creatinine doubling time) was calculated by linear regression analysis of 1/creatinine in 11 Chinese herbs nephropathy patients and in 11 control patients with an initial serum creatinine below 3.5 mg/dl.

The characteristics of the Chinese herbs nephropathy and control groups at presentation were compared by Student's *t*-test or chi-square test as needed. The kidney survival rate was calculated according to Kaplan and Meier, the two groups being compared by the log-rank test. Differences were considered significant for $P<0.05$.

Results

Features at presentation

The characteristics at the time of diagnosis of Chinese herbs nephropathy are presented in Table 1.

All Chinese herbs nephropathy patients were women, aged 27–59 (mean 41 years) with an initial serum creatinine level ranging from 1.35 to 9.1 mg/dl.

Twelve patients had hypertension, usually mild to moderate. Mean blood pressure exceeded 130 mmHg in only three cases, and a single patient had a stage 3 retinopathy at the first visit. Chinese herbs nephropathy patients had significant anaemia (range 5.9–12.8 g/dl) and mild proteinuria, of tubular type (range 120–2370 mg/day). Urinalysis disclosed glycosuria without hyperglycaemia in 40% and aseptic leukocyturia in 40% of the patients. The sediment was otherwise normal in 46% of the patients.

Kidney tomography displayed kidneys smaller than 13 cm in 85% of the cases and asymmetric kidneys in 54% (longitudinal axes of the kidneys differing by >1 cm). Kidney outlines were irregular in 31% of the cases. Bilateral ureterohydronephrosis due to extensive periureteral fibrosis was observed in one case [7].

Renal biopsy obtained in two patients demonstrated characteristic diffuse interstitial fibrosis without cellular infiltrate.

One patient presented with liver and kidney cysts at ultrasonography but normal sized kidneys. A 62-year-old maternal aunt was known to have renal and hepatic cysts. The diagnosis of Chinese herbs nephropathy superimposed on autosomal dominant polycystic kidney disease (ADPKD) was retained. Pathology of one kidney removed subsequently at renal transplantation disclosed multiple cysts compatible with incipient ADPKD and extensive tubulointerstitial fibrosis similar to that observed in other cases of Chinese herbs nephropathy.

In another patient who had no haematuria and only mild proteinuria at presentation, pathology of one kidney removed during transplantation disclosed significant mesangial IgA deposits without mesangial proliferation in addition to the characteristic intense acellular interstitial fibrosis. The diagnosis of Chinese herbs nephropathy superimposed on IgA nephropathy was retained.

Table 1. Comparison between Chinese herbs nephropathy group and control group at presentation (mean ± SD)

	Chinese herbs nephropathy group ($n=15$)	Control group ($n=15$)	*P* value
Sex	15F	15F	
Age (years)	41 ± 10	34 ± 13	NS
Serum creatinine (mg/dl)	2.9 ± 2.5	3.2 ± 1.7	NS
Systolic blood pressure (mrnHg)	158 ± 25	141 ± 20	NS
Diastolic blood pressure (mmHg)	95 ± 13	89 ± 11	NS
Mean blood pressure (mmHg)	116 ± 17	106 ± 12	NS
Haemoglobin (g/dl)	10.2 ± 1.7	12.2 ± 1.6	<0.002
Plasma HCO_3 (mmol/1)	23 ± 3.9	22 ± 3.2	NS
Proteinuria (mg/24 h)	657 ± 574	1624 ± 819	<0.009
Urinary sediment	Normal = 7/15 Glycosuria = 6/15 leukocyturia = 6/15 (>5 WBC/HPF)	Normal = 7/15 Glycosuria = 5/15 leukocyturia = 7/15	
Aortic insufficiency on echocardiography	5/12	0/12	$P<0.05$

Doppler echocardiography showed mild aortic insufficiency in six of the 13 tested patients. None of the patients had fluid overload at the time of echocardiography. After exclusion of the patient with ADPKD and aortic insufficiency because of the known association of valvular disease with ADPKD, the prevalence of aortic insufficiency was 42% (5/12).

No other cause of aortic insufficiency such as rheumatic fever, rheumatoid arthritis, or ankylosing spondylitis was present.

Comparison with control group

The control group included 15 women with an age range and initial serum creatinine similar to that of the Chinese herbs nephropathy group. Doppler echocardiography was normal in all control patients. The Chinese herbs nephropathy group exhibited a significantly lower proteinuria, more severe anaemia, and higher prevalence of aortic insufficiency than the control group (Table 1).

Follow up

Treatment

Arterial hypertension was treated by ACE inhibitors ($n=10$), calcium-channel blockers ($n=1$) and beta blockers ($n=1$). Mean blood pressure was maintained below 110 mmHg for eight patients and between 110 and 120 for the four others throughout the follow-up. Additional treatment included a low-salt low-protein diet, oral $CaCO_3$, and subcutaneous erythropoietin when appropriate. No steroids were given.

Renal survival

The time required for serum creatinine to increase by 100% (creatinine doubling time) was calculated in the 12 patients with Chinese herbs nephropathy and an initial creatinine below 3.5 mg/dl. One of them was not included as her serum creatinine remained stable during a 1-year follow-up (creatinine doubling time impossible to calculate). Results were compared with those of the 11 matched control patients.

Creatinine doubling time was significantly shorter in the Chinese herbs nephropathy group ($n=11$) (13 ± 9 months) than in the control group ($n=11$) (52 ± 31 months) ($P<0.05$). The 2-year actuarial renal survival of the Chinese herbs nephropathy group proved significantly worse (17%) than that of the control group (74%) (Figure 1) ($P=0.017$), confirming thus that renal failure progressed faster in the Chinese herbs nephropathy than in the control group.

Among the 10 Chinese herbs nephropathy patients who reached ESRD, five remain on chronic haemodialysis and five have been transplanted by 30 June 1995.

Features influencing individual progression rate of renal failure were evaluated:

(a) *Delay between the end of Chinese herbs ingestion and the diagnosis of Chinese herbs nephropathy (free interval).* As illustrated in Figure 2, duration of free interval was correlated with creatinine doubling time ($n=11$) ($r=0.715$; $P=0.013$). Patients detected between October 1991 and June 1992, i.e. with a short free interval ($n=5$), developed subacute renal failure and were all on renal replacement therapy (RRT) by 1 February 1993, within 1–15 (mean 6.6) months of Chinese herbs nephropathy diagnosis. By contrast, patients included between July 1993 and June 1994, i.e. with a long free interval ($n=4$), had a slower progression of renal failure: none was on RRT at the end of June 1995. The intermediate group diagnosed between July 1992 and June 1993 ($n=6$), showed an intermediate progression rate of renal failure: all but one have reached ESRD before 30 June 1995 within 9–21 (mean 15.8) months; the sixth patient has a serum creatinine of 5 mg/dl on 30 June 1995.

(b) *The duration of Chinese herbs treatment.* Assessment of the actual amount of ingested herbs was difficult as patient recollection of the number of daily pills as well as the quantity included in each pill were imprecise. As a surrogate marker of the amount of Chinese herbs ingested, we therefore relied on the duration of treatment between May 1990 and July 1992, the period during which Chinese herbs were included in the slimming pills.

The duration of Chinese herbs treatment proved

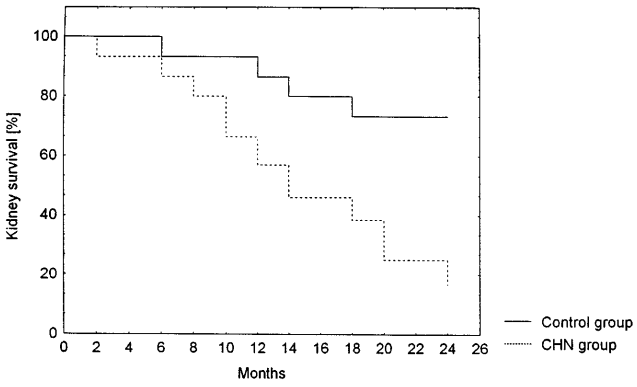

Fig. 1. Kaplan–Meier actuarial kidney survival in 15 Chinese herbs nephropathy and 15 control patients with chronic interstitial nephritis ($P=0.017$).

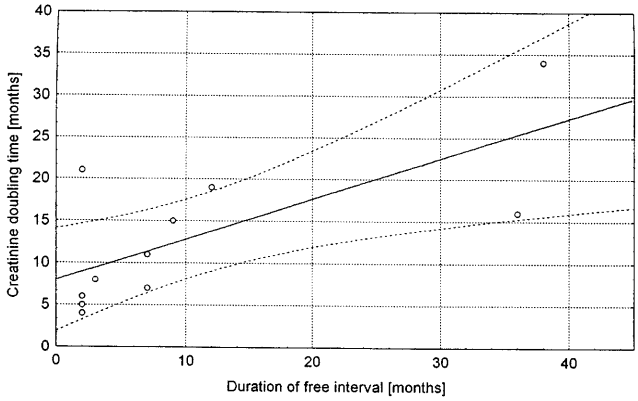

Fig. 2. Relation between free interval duration and time needed to double serum creatinine ($n=11$, $r=0.715$, $P=0.013$).

inversely related to the duration of the free interval (Figure 3) ($r=-0.769$; $P=0.006$, $n=11$) and to creatinine doubling time ($r=-0.631$; $P=0.037$, $n=11$) (Figure 4).

(c) *Hypertension.* Presence of hypertension at presentation did not influence prognosis: three patients with normal blood pressure at presentation had a rapid progression of renal failure (all in the first group with short interval). Control of blood pressure during follow-up was not significantly better in the group with a long free interval than in the intermediate group: mean arterial blood pressure 107 mmHg *versus* 113 mmHg respectively.

Post-transplantation evolution

Five patients received a renal transplant (2 from living and 3 from cadaveric donors) between September 1992 and January 1994.

Maintenance immunosuppressive regimen included in all patients cyclosporin, azathioprine, and prednisolone.

Neither acute tubular necrosis nor acute rejection episodes were observed. Serum creatinine rose slowly from 1.6 mg/dl to 2.5 mg/dl in one patient. A biopsy of the graft performed after 9 months showed mild lesions of chronic rejection without evidence of recurrence of Chinese herbs nephropathy.

In the group of five patients, serum creatinine averaged 1.37 mg/dl after 6 months and 1.48 mg/dl after 1 year.

The pattern of low-molecular-weight proteinuria observed in Chinese herbs nephropathy [6] was absent in all four tested patients. There is thus no evidence for recurrence of the disease after transplantation.

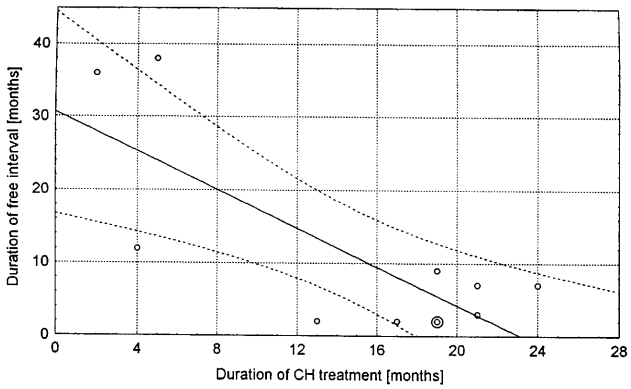

Fig. 3. Relation between the duration of Chinese herbs treatment and duration of free interval ($n=11$; $r=-0.769$, $P=0.006$).

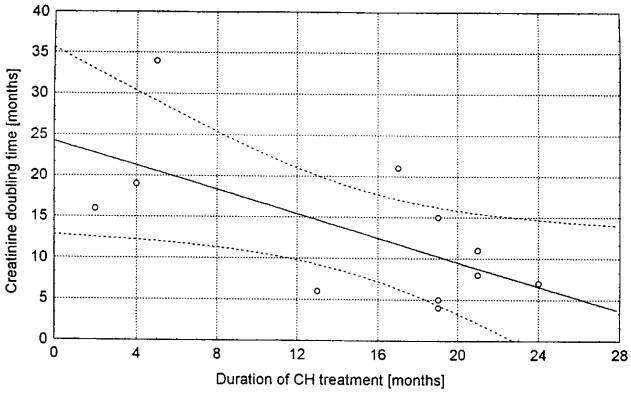

Fig. 4. Relation between the duration of Chinese herbs treatment and time needed to double serum creatinine ($n=11$) ($r=-0.631$; $P=0.037$).

Complications

One patient presented with macroscopic haematuria due to papillary transitional-cell carcinoma of the bladder, 27 months after the slimming cure (11 months after kidney transplantation). A ureteronephrectomy of the remnant kidney was performed and disclosed microinvasive urothelial carcinoma of the ureter. Four months later the patient developed two new papillary bladder tumours, removed by cystoscopy. In another patient, *in situ* urothelial carcinoma was found in the native ureter removed during kidney transplantation.

One patient developed acute orthopnoea and dyspnoea 35 months after the slimming cure and 12 months after initiation of dialysis. Echocardiography showed severe aortic and mitral insufficiencies. At surgery, marked thickening of the aortic valve, with secondary mitral dilatation was found. Bivalvuloplasty was successfully performed.

Two patients developed severe anaemia, one 6 months after the ingestion of Chinese herbs (haemoglobin 6.9 g/dl with a creatinine of 2.3 mg/dl), another 17 months after the ingestion of Chinese herbs and 1 month after kidney transplantation (haemoglobin 6.7 g/dl and creatinine 1.32 mg/dl). In both cases biopsy showed a hypoplastic bone marrow.

The serious complications described above (urothelial carcinomas, cardiac insufficiency due to aortic regurgitation, severe anaemia, bilateral ureterohydronephrosis) were observed only in the patients with a short free interval.

Discussion

Chinese herbs nephropathy has been recognized only recently in a limited group of women who had attended a single X slimming clinic in Brussels and had ingested, between 1990 and 1992, pills containing two Chinese herbs, *Stephania tetrandra* and *Magnolia officinalis* [1].

As initial toxicological investigations performed on batches of Chinese herbs failed to show the presence of tetrandrine, an alkaloid characteristic of *Stephania tetrandra* [1], it was hypothesized that *Stephania tetrandra* (Fangji) had been inadvertently replaced by aristolochia (Fangchi). Aristolochic acid was indeed found subsequently in batches of Chinese herbs [8].

The pathological aspects of Chinese herbs nephropathy are characteristic [2,3]. They consist of extensive paucicellular interstitial fibrosis with atrophy and loss of tubules decreasing from the outer to the inner

cortex. The glomeruli are relatively spared. Mild to moderate atypia and atypical hyperplasia of the urothelium were also observed and two cases of urothelial malignancy have been described [4,5].

In this paper we provide the first detailed description of the initial clinical, biochemical, and radiological features as well as of the natural history of the disease and compare it with a control group of patients with chronic interstitial nephritis of other causes.

Typically, patients present with moderate hypertension and mild proteinuria of tubular origin. Glycosuria and aseptic leukocyturia were present in 40% of the cases.

Anaemia was more severe than expected for the degree of renal failure, perhaps as a result of an early destruction of cortical peritubular cells producing erythropoietin. Other causes of anaemia were excluded (haemolysis, iron deficiency).

The kidneys were shrunk, asymmetric in 54% of the cases, with irregular outlines in 31% of the cases.

The fibrotic process may extend beyond the kidneys as suggested by the presence of unexplained periureteral fibrosis in one case [7] and of marked submesothelial fibrosis of the peritoneal membrane in two Chinese herbs nephropathy patients on peritoneal dialysis [9]. The presence of aortic insufficiency in 42% of the cases, with eventual surgery in one, is of great interest. No such case was observed in the control group. Neither hypervolaemia nor any known cause of aortic insufficiency was present. The marked thickening of the aortic valve observed by the surgeon in one case suggests that aortic insufficiency might be another example of the extrarenal manifestations of Chinese herbs intoxication.

A striking feature of Chinese herbs nephropathy is its subacute course: progression to ESRD is indeed faster in Chinese herbs nephropathy than in other interstitial nephropathies, the 2-year actuarial survival rate without ESRD being 17% in the Chinese herbs nephropathy group *versus* 74% in the control group. Within the Chinese herbs nephropathy group, progression rate proved inversely related to the duration of Chinese herbs treatment and to the free interval between the end of Chinese herbs exposure and the detection of renal disease. Three patients who had ingested a small quantity of Chinese herbs developed mild renal failure only 3 years after the end of the slimming regimen.

The delayed onset as well as progression of renal failure up to several years after interruption of the toxic substance suggest that Chinese herbs exert their action through mechanisms at least partially independent of direct cytotoxicity.

The discovery, in the renal tissue of five of our patients, of DNA adducts of aristolochic acid, one of the compounds suspected in the genesis of Chinese herbs nephropathy [10], raises the possibility that Chinese herbs nephropathy might be related to DNA modifications that might take years to express themselves. It is of interest to remember that aristolochic acid DNA adducts have also been associated in cancerous forestomach tumours of rats fed aristolochic acid with base substitutions in the 'ras' oncogene sequences [11–13]. Within this framework the presence of cellular atypias in the urothelium as well as the recognition of urothelial tumours in our patients are noteworthy.

It is also of interest that the disease did not recur after transplantation, although this requires confirmation in view of the small number of TP patients followed for a relatively short period.

Treatment modalities of Chinese herbs nephropathy remain to be discussed. We tried to influence the course of the disease by relying on angiotensin-converting enzyme inhibitors not only to return blood pressure to normal values but also with an eye to the possibility of slowing the production of TGFb, a cytokine incriminated in fibrotic processes and known to be stimulated by angiotensin II [14]. In the absence of a prospective control group we cannot speculate on the efficacy of this approach. It appears certain, however, that it was unable to prevent progression. In view of the usually paucicellular aspect of the interstitial fibrosis we have chosen to refrain from steroid therapy. Another group has recently reported that steroid therapy slowed the deterioration of renal function [15]. Twelve patients with a serum creatinine <4 mg/dl at presentation, given steroid therapy, were retrospectively compared with 23 patients not given any specific treatment. Complications of steroids were substantial as six of the 12 treated patients experienced one or more severe side-effects. The progression rate of our 12 patients with a serum creatinine <4 mg/dl at presentation is intermediate between that reported for steroid-treated and untreated patients. Serum creatinine averaged 2.5, 2.6 and 2.8 mg/dl at the onset in our patients and in the untreated and steroid-treated groups respectively. These values reached respectively 4.2, 5.3 and 2.9 at 6 months and 6.1, 7.1 and 4 mg/dl at 1 year.

An analogy between Balkan endemic nephropathy and Chinese herbs nephropathy has been suggested on the basis of the histological aspects, the presence of urothelial atypias, and the existence of a possible common aetiological factor: aristolochic acid intake [2]. Several of our results lend further support to this suggestion: the presence of mild hypertension, more pronounced anaemia, and tubular proteinuria are also characteristic of Balkan nephropathy. The difference in progression rates according to Chinese herbs intake suggests further that the much slower evolution of Balkan endemic nephropathy might reflect a very low but sustained intake of aristolochic acid. Chinese herbs nephropathy, although a tragic event for the patients, teaches us lessons not only about drug regulations and social attitudes towards medicine [16] but also on the epidemiology and the pathogenesis of renal diseases.

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