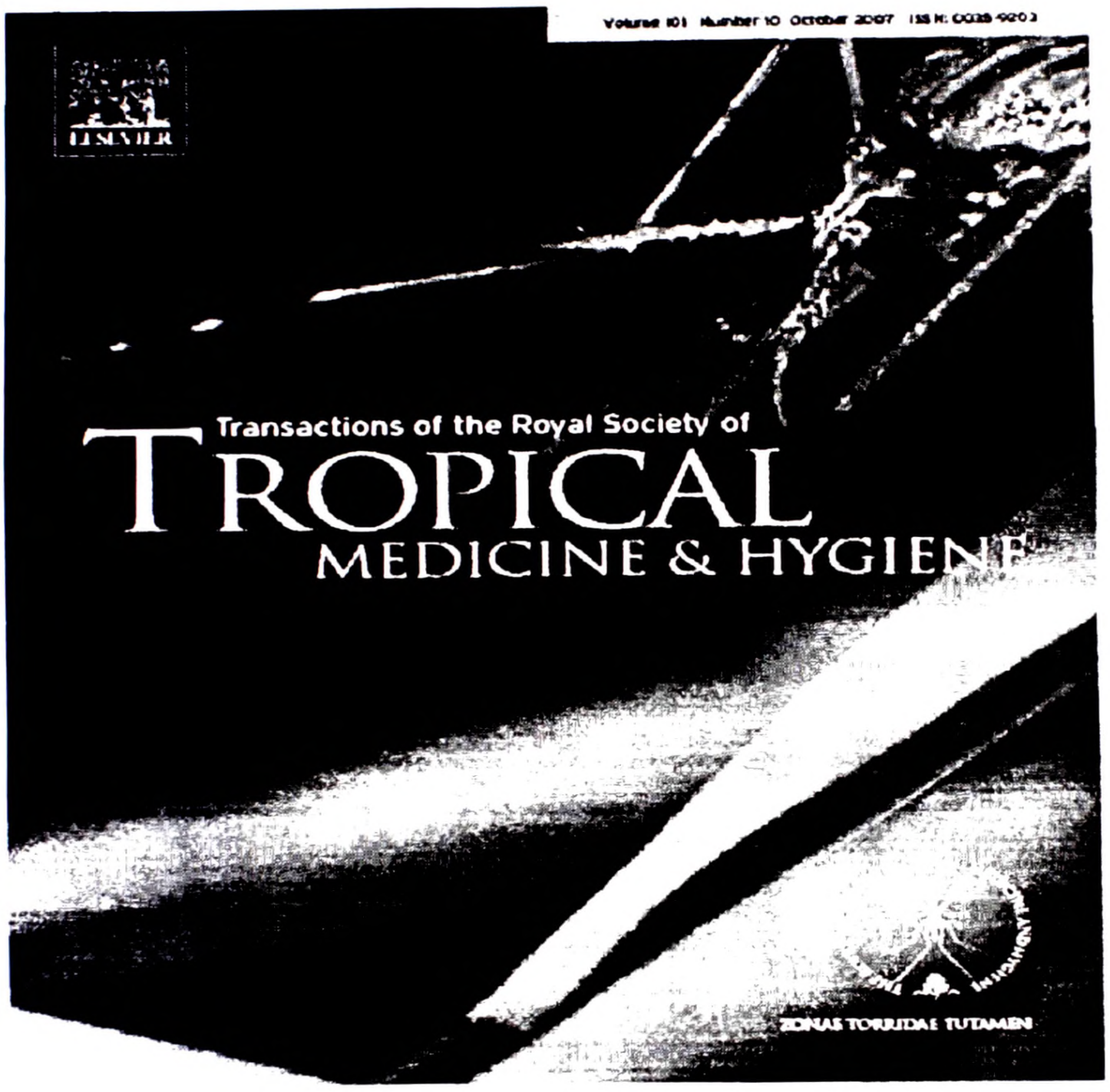
3.2 CHRONIC RENAL FAILURE IN NORTH CENTRAL PROVINCE OF SRILANKA :AN ENVIRONMENTALLY INDUCED DISEASE



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Chronic renal failure in North Central Province of Sri Lanka: an environmentally induced disease

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Summary This study was conducted to determine the aetiology of chronic renal failure (CRF) in the North Central Province of Sri Lanka. Patients (n= 183) with CRF of unknown aetiology were compared with controls (n= 200) who had no evidence of chronic renal dysfunction. Exposure to possible risk factors were determined by an interviewer-administered questionnaire. Being a farmer (P< 0.001), using pesticides (P< 0.001), drinking well water (P< 0.001), a family history of renal dysfunction (P= 0.001), use of ayurvedic treatment (P< 0.001) and a history of snake bite (P< 0.001) were risk factors for CRF of unknown aetiology. Using logistic regression analysis, a family history of chronic renal disease, taking ayurvedic treatment and history of snake bite were found to be significant predictors for CRF of unknown aetiology. There is evidence to support an environmental aetiology to CRF in Sri Lanka.

1. Introduction

Chronic renal failure (CRF) is emerging as a major health problem in Sri Lanka. Although the precise figures are not known, the growing numbers of patients suffering from CRF place a great demand on the health care resources of the country, due to the high cost of dialysis and transplantation. The causes and risk factors for the development of CRF vary worldwide. Diabetes, hypertension and reno-vascular diseases are the common causes of CRF in developed countries, whereas glomerular diseases related to infections are common in tropical areas (D'Amico, 1987; Port, 1995; Ritz et al., 1999). In the majority of patients with CRF the underlying cause remains unknown.

The incidence of CRF can vary with geographical area within the same country. Recent reports have highlighted an increased incidence of CRF in the North Central Province of Sri Lanka (Hittarage, 2004). The North Central Province of Sri Lanka is part of the dry zone of the country and is

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predominantly an agricultural area. The province extends over 10 530 m^3 of land, which includes dry tropical woodlands. In 2001 CRF was the leading cause of death at the Anuradhapura General Hospital, the main tertiary care hospital of the province, according to the hospital's statistics. The number of hospital admissions and mortality due to CRF has increased in the same hospital during the past 10 years (General Hospital, Anuradhapura, 2001). In most of these patients the underlying cause for chronic renal failure is unknown. Unrecognized environmental toxins or occupational exposures may lead to chronic kidney disease, but this remains unproven. As the majority of these patients are from the farming community, it has been argued that chronic pesticide exposure could be a risk factor for the development of CRF. The objective of the current study was to determine the aetiology of CRF in the North Central Province of Sri Lanka.

2. Materials and methods

One hundred and eighty-three patients with CRF of unknown aetiology were recruited randomly from among patients presenting to the renal clinic at the Teaching Hospital, Anuradhapura (n= 136 males and n= 47 females). Patients with a serum creatinine concentration greater than 2 mg/dl with no obvious underlying cause detected by investigations were selected. Those who had a definite aetiological factor for CRF, e.g. obstructive uropathy, diabetes or hypertensive nephropathy, were excluded from the study. A control group of 200 subjects (n= 139 males and n= 61 females) in the age group 36–67 years, corresponding to the age groups of the cases and having no evidence of CRF, were randomly recruited from among patients with hypertension, diabetes mellitus etc. from the general medical clinic of the same hospital. All subjects were recruited after obtaining informed written consent.

A structured interviewer-administered questionnaire was used to obtain information about personal details, occupational history and exposure to possible risk factors for CRF. The risk factors assessed were occupation and pesticide handling, family history of renal disease, source of drinking water at home and in the field, history of use of ayurvedic treatment continuously for a period of 1 month or more before the onset of CRF, and a history of snake bite. The questionnaire was pre-tested.

Data were double-entered and analysed using SPSS (SPSS Inc., Chicago, IL, USA). Associations between variables were tested using independent samplettests, χ^2 tests, Fisher's exact tests and odds ratios. Ninety-five percent confidence intervals were calculated for the odds ratios. Backward logistic regression was used to control for confounding factors.

3. Results

Male patients with chronic renal disease were older than the controls, but the females in the two groups were of similar age (Table 1). The mean height and weight were similar in both groups among both males and females. The majority of the patients were farmers or were actively involved in farming activities (86 and 62% of males and females, respectively).

Among the males, being a farmer, having used pesticides, drinking water from the well in the field, having a family history of renal dysfunction, taking ayurvedic treatment in the past and a past history of snake bite were more common among patients with CRF compared with controls (Table 2). Among the females, the risk of exposure to well water at home and snake bites was higher among patients with CRF of unknown aetiology compared with the controls (Table 2).

Considering both males and females together, being a farmer, using pesticides, drinking well water at home and in the field, having a family history of renal dysfunction, having taken ayurvedic treatment in the past and a past history of snake bite were risk factors of CRF of unknown aetiology (Table 2). Pesticide poisoning in the past (P= 0.285), drinking water from streams (P= 0.477) and tube wells (P= 0.873) for home consumption, using drinking water taken from home for use in the field (P= 0.277) and having hypertension (P= 0.710) were not risk factors for CRF. Diabetes mellitus was more common among the controls compared with the patients with CRF.

In a multivariate logistic regression analysis, a family history of chronic renal dysfunction, a history of having taken ayurvedic treatment and having had a snake bite in the past were significant predictors of CRF of unknown aetiology (Table 3). Subjects with a family member with renal dysfunction were 4.5 times more likely to have CRF of unknown aetiology compared with those without such a family history. Subjects who had taken ayurvedic treatment and had a history of snake bite were approximately 2.5 times more likely to have chronic renal failure of unknown aetiology compared with those without such a history.

Table 1 Selected characteristics of the cases (n= 183; 136 males and 47 females) and controls (n= 200; 139 males and 61 females)

Variable	Sex	Mean (SD)		P-value
		Cases	Controls	
Age (years)	Males	56.73 (12.25)	51.10 (14.70)	0.001
	Females	54.22 (12.50)	53.67 (12.42)	0.812
Height (cm)	Males	161.38 (18.66)	161.42 (11.31)	0.981
	Females	151.16 (6.65)	150.25 (7.00)	0.472
Weight (kg)	Males	57.67 (21.29)	56.53 (13.09)	0.587
	Females	51.56 (17.57)	53.24 (10.59)	0.524

Table 2 Comparison of selected variables among patients with chronic renal disease of unknown aetiology (cases) and those without chronic renal disease (controls)

Variable		No. (%) females		No. (%) males		Total (%)	
		Cases (n=47)	Controls (n=61)	Cases (n=136)	Controls (n=139)	Cases (n=183)	Controls (n=200)
Farmers	Yes	29(62)	34 (56)	117(86)	79 (57)	146(80)	113 (57)
	No	18(38)	27 (44)	19(14)	60 (43)	37(20)	87 (43)
χ^2 (P-value)[a]		0.39 (0.553)		28.62 (<0.001)		23.66 (<0.001)	
Odds ratio (95% CI)		1.28 (0.55–2.99)		4.68 (2.50–8.82)		3.04 (1.88–4.92)	
Used pesticides	Yes	–	3 (5)	98(72)	65 (47)	98(54)	68 (34)
	No	47(100.0)	58 (95)	38(28)	74 (53)	85(46)	132 (66)
Test statistic (P-value)		(0.176)[b]		18.22 (<0.001)[a]		14.88 (<0.001)[a]	
Odds ratio (95% CI)		–[c]		2.94 (1.73–5.01)		2.24 (1.45–3.45)	
Water source at home							
Well	Yes	40(85)	35 (57)	113(83)	103 (74)	153(84)	38 (69)
	No	7(15)	26 (43)	23(17)	36 (26)	30(16)	62 (31)
χ^2 (P-value)[a]		9.62 (0.001)		3.30 (0.069)		11.17 (<0.001)	
Odds ratio (95% CI)		4.24 (1.51–12.32)		1.72 (0.92–3.22)		2.29 (1.36–3.87)	
Pipeborne	Yes	3(6)	13 (21)	5(4)	23 (16)	8(4)	36 (18)
	No	44(94)	48 (79)	131(96)	116 (84)	175(96)	164 (82)
Test statistic (P-value)		(0.030)[b]		12.45 (<0.001)[a]		17.45 (<0.001)[a]	
Odds ratio (95% CI)		0.25 (0.05–1.04)		0.19 (0.06–0.56)		0.21 (0.09–0.48)	
Water source in field:							
Well	Yes	2(4)	2 (3)	15(11)	6 (4)	17(10)	8 (4)
	No	45(96)	59 (97)	121(89)	133 (96)	166(90)	192 (96)
Test statistic (P-value)		(0.586)[b]		4.39 (0.036)[a]		4.38 (0.036)[a]	
Odds ratio (95% CI)		1.31 (0.13–13.68)		2.75 (0.96–8.22)		2.46 (0.97–6.39)	
Diabetes mellitus	Yes	5(11)	24 (39)	13(10)	31 (22)	18(10)	55 (27)
	No	42(89)	37 (61)	123(90)	108 (78)	165(90)	145 (73)
χ^2 (P-value)[a]		11.14 (<0.001)		8.31 (0.003)		19.33 (<0.001)	
Odds ratio (95% CI)		0.18 (0.05–0.58)		0.37 (0.17–0.78)		0.29 (0.15–0.53)	
Glomerular nephritis	Yes	2(4)	–	7(5)	–	9(5)	–
	No	45(96)	61 (100)	129(95)	139 (100)	174(95)	200 (100)
Fisher's exact test (P-value)		(0.187)		(0.006)		(0.001)	
Odds ratio (95% CI)[c]		–		–		–	
Chronic renal disease in the family	Yes	4(8)	4 (7)	15(11)	1 (1)	19(10)	5 (2)
	No	43(92)	57 (93)	121(89)	138 (99)	164(90)	195 (98)
Test statistic (P-value)		(0.488)[b]		(<0.001)[b]		10.11 (0.001)[a]	
Odds ratio (95% CI)		1.44 (0.57–3.64)		17.11 (2.32–352.3)		4.52 (1.55–14.15)	
Taken ayurvedic treatment	Yes	15(32)	15 (25)	46(34)	20 (14)	61(33)	35 (17)
	No	32(68)	46 (75)	90(66)	119 (86)	122(67)	165 (83)
χ^2 (P-value)[a]		0.71 (0.399)		11.244 (<0.001)		12.75 (<0.001)	
Odds ratio (95% CI)		3.50 (1.10–11.56)		3.04 (1.62–5.75)		2.36 (1.42–3.91)	
History of snake bite	Yes	13(28)	6 (10)	36(26)	18 (13)	49(27)	24 (12)
	No	34(72)	55 (90)	100(74)	121 (87)	134(73)	176 (88)
χ^2 (P-value)[a]		5.82 (0.015)		7.96 (0.004)		13.52 (<0.001)	
Odds ratio (95% CI)		1.33 (0.26–6.78)		2.42 (1.24–4.74)		2.68 (1.58–4.76)	

[a] Yates'-corrected χ^2 value.
[b] Fisher's exact test (P-value).
[c] Odds ratio (95% CI) not calculated due to zero cells.

4. Discussion

The significant predictors of renal failure of unknown aetiology are a family member with renal dysfunction, a history of taking ayurvedic treatment and snake bite in the past. A family history with renal dysfunction suggests a genetic aetiology of the disease. However, given that only individuals in families living in this area develop the disease, it is

Table 3 Summary results of logistic regression analysis

Variable	Regression coefficient	*P*-value	Odds ratio (95% CI)
Intercept	−0.182		
Family history of renal disease[a]	1.523	0.018	4.588 (1.297–16.228)
Taken ayurvedic treatment[b]	0.919	0.003	2.508 (1.369–4.596)
History of snake bite[c]	0.881	0.009	2.414 (1.256–4.678)

[a] Reference category is no family history of renal disease.
[b] Reference category is having not taken any ayurvedic treatment.
[c] Reference category is no history of snake bite.

highly likely that the disease is triggered by an environmental factor in those genetically predisposed.

A past history of taking ayurvedic treatment and snake bite may also be aetiologic factors for CRF. Most ayurvedic preparations are not standardized and may have unknown compounds that result in CRF. Chronic interstitial nephritis due to ingestion of the Chinese herb *Stephania tetrandra* in a slimming regimen was described in Brussels, Belgium in 1993 (Kabanda et al., 1995). The withdrawal of this herb from the market caused a marked reduction of CRF in the population of the affected area. Snake bite is a recognized cause of acute renal failure, and severe envenomation causing cortical necrosis can lead to CRF. However, in the current study, only three out of a total of 49 patients with CRF who reported snake bite in the past had envenomation severe enough to be treated in hospital. The number of hospital admissions due to snake bite in the country in year 2000 alone was 37 081 (Ministry of Health, 2000). Given the wide use of ayurvedic preparations in most parts of the country, and the incidence of snake bites in other parts of the country, the magnitude of the incidence of CRF in the North Central Province is difficult to explain by these two factors.

Glomerulonephritis is among the leading causes of CRF in many parts of the world. Few patients in the study population reported clinical features suggestive of glomerulonephritis in the past ($n=9$; 4.9% of the cases). Renal biopsies done in patients diagnosed as early stages of chronic kidney disease did not support the diagnosis of post-infectious glomerulonephritis or IgA nephropathy. Other infections leading to renal disease, such as *Plasmodium malariae*, schistosomiasis and visceral leishmaniasis have not been reported in Sri Lanka. Malaria due to *P. falciparum* and *P. vivax* is endemic in the dry zone of Sri Lanka, including the North Central Province. Glomerulonephritis has been documented in *P. falciparum* infection, but to date in Sri Lanka there has been no evidence to support progression to chronic kidney disease.

Diabetes mellitus was found to be a significant risk factor in bivariate analysis, with controls having a higher prevalence. However, in the multivariate analysis, when adjusted for other factors, diabetes was not a significant predictor of CRF, probably due to the fact that the prevalence of diabetes was more common among the controls compared with the cases.

As pesticides are commonly used in the area, there is serious concern whether exposure to pesticides is an aetiological factor for CRF. Evidence of greater inhibition of acetylcholinesterase among patients with chronic renal dysfunction in the same study area compared with patients with chronic renal dysfunction from non-agricultural areas of the country has been reported (Peiris-John et al., 2006). Although initial analysis indicated that being a farmer and use of pesticides were associated with CRF, in the multivariate model these variables were excluded (Table 2). This clearly dismisses the hypothesis that long-term low-level (occupational or environmental) exposure to pesticides has an impact on the development of CRF.

Although drinking well water both from home and the field was a significant predictor of CRF univariately, in the multivariate model it was not significant. If it had been significant it would have provided unequivocal evidence of an environmental aetiology. It is likely that drinking well water was associated with a family history of renal dysfunction, and as a result it was excluded from the model. The Dry Zone of Sri Lanka has several areas in which the ground water is high in mineral content and rich in fluoride. It has also been shown that the dissolution of aluminium from poor-quality cooking utensils is high in the presence of fluoride in the water. The village folk use aluminium pots and utensils to store and boil water (Herath et al., 2005). Hence, we still propose the hypothesis that the high incidence of CRF of unknown aetiology in the North Central Province of Sri Lanka is probably due to an environmental factor, with the clustering of cases within families being due to a possible genetic predisposition to the potential environmental factor.

Several environmentally induced kidney diseases have been described in the literature (Ascher, 2003; Buchet et al., 1990; Peiris-John et al., 2006; Tatu et al., 1998). Chronic heavy metal toxicity, such as that from lead and mercury, is known to cause chronic renal damage. Severe hypertension, gout and behavioral changes characteristic of lead nephropathy have not been observed in the patients with CRF in the North Central Province. Cadmium is another heavy metal associated with renal disease (Buchet et al., 1990). Industrial cadmium poisoning of several rivers in Japan caused contamination of locally produced rice, causing 'Itai-itai disease' characterized by renal calculi and painful osteomalacia.

Balkan endemic nephropathy (BEN) is a chronic kidney disease prevalent among settlers along the tributaries of the Danube River in Serbia, Bosnia, Bulgaria and Romania (Stefanovic, 1998). First described in 1957, BEN is a slowly progressive tubulo-interstitial disease leading to end-stage renal failure. This disease has several factors similar to those of renal failure patients from the North Central Province, including the fact that the disease affects predominantly farmers, a familial aggregation of cases and interstitial nephropathy seen in renal biopsy (Hittarage, 2004). However, the increased incidence of tumours of the renal pelvis and ureter described in BEN has not been

reported in our study population. BEN has attracted the interest of researchers as a possible environmental disease, and many environmental and genetic factors have been evaluated as possible underlying causes (Ascher, 2003; Buchet et al., 1990). One hypothesis considers that mycotoxins ingested in small amounts by individuals in the endemic regions might initiate the renal damage. Another theory considers the exposure to aromatic hydrocarbons leaching into well water in endemic areas as an aetiologic factor (Tatu et al., 1998).

The aetiology of chronic renal failure in the North Central Province of Sri Lanka still remains unknown. The current study strongly supports an environmentally induced disease. Further investigations should focus on environmental factors and on the role of genetic factors.

Authors' contributions: KPW, RJPJ, RW and AH designed the study protocol; KPW and AH carried out the data collection; RW and RJPJ carried out the analysis and interpretation of the data. All authors drafted the manuscript and read and approved the final version. KPW is guarantor of the paper.

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