ANALGESIC NEPHROPATHY – A PROSPECTIVE STUDY

M. SEGASOTHY
BETTY KONG CHIEW TONG
A. KAMAL
ZAKI MURAD
ABU BAKAR SULEIMAN

SUMMARY

A prospective study was performed on patients admitted to the medical and renal wards of General Hospital, Kuala Lumpur. Over a period of 14 months from 1 January 1982, 12 new cases of analgesic nephropathy (AN) were documented. Contrary to the experience in the West and in Australia, AN in Malaysia tends to have a male preponderance and occurs even in the younger age groups. The common analgesics abused are paracetamol, Chap Kaki Tiga and Chap Harimau. The main reasons for analgesic abuse are headache and arthritis. In addition to radiological features of renal papillary necrosis patients have the other manifestations of the disease such as peptic ulceration, anaemia, neuro-psychiatric disorders and ischaemic heart disease.

M. Segasothy, MRCP (UK)
Department of Medicine
Faculty of Medicine
Universiti Kebangsaan Malaysia, Kuala Lumpur

Betty Kong Chiew Tong, MBBS (Mon)
Nephrology Unit
General Hospital
Kuala Lumpur

A. Kamal, DMRD, FFRRCS (Ire), FRCR (Eng)
Department of Radiology
Faculty of Medicine
Universiti Kebangsaan Malaysia

Zaki Murad, MRCP (UK)
Nephrology Unit
General Hospital
Kuala Lumpur

Abu Bakar Suleiman, MBBS (Mon), M.Med, FRACP
Nephrology Unit
General Hospital
Kuala Lumpur

INTRODUCTION

Analgesic nephropathy occurs most commonly in Australia, Switzerland and Sweden. Many European countries have an intermediate incidence and it is relatively rare in South America, Middle-East, India and Japan. In the US, it seems to be surprisingly uncommon. [1] As no figures are available for Malaysia, we did a prospective study to determine the incidence of AN.

MATERIALS AND METHOD

From 1 January 1982, patients admitted to the medical and renal wards at the General Hospital, Kuala Lumpur were questioned as to whether they consume analgesics and if so, the type, quantity, frequency, duration and the reason for consumption of analgesic was ascertained.

Patients who admitted to taking analgesics regularly were also questioned as to whether they consume other drugs like laxatives and alcohol and as to whether they smoke cigarettes. These patients were also assessed psychologically to determine if they had depression, anxiety neurosis, inadequate personality or any other mental aberration.

The following investigations were done on them: haematological profile, renal profile, liver profile, 24 hours urine for protein, urine concentration test, ammonium chloride acidification test in patients whose renal profile was normal and an intravenous urogram (IVU). Where indicated urine was

examined for acid-fast bacilli and cultures were done.

RESULTS

From January 1982 to February 1983, forty patients were found to have been taking analgesics regularly. We managed to perform most of the above mentioned investigations including the IVUs in only thirty patients as the others were lost to follow up. Twelve of these patients had radiological evidence of renal papillary necrosis (Figs. 1-3).

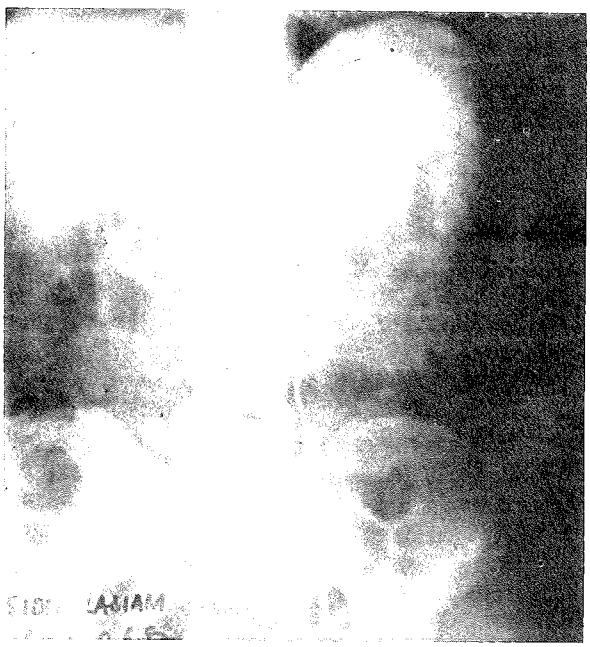

Fig. 1a Left retrograde pyelogram: Blunting of the papillae noted. In addition, a low density calculus is noted in the lower pole calyx.

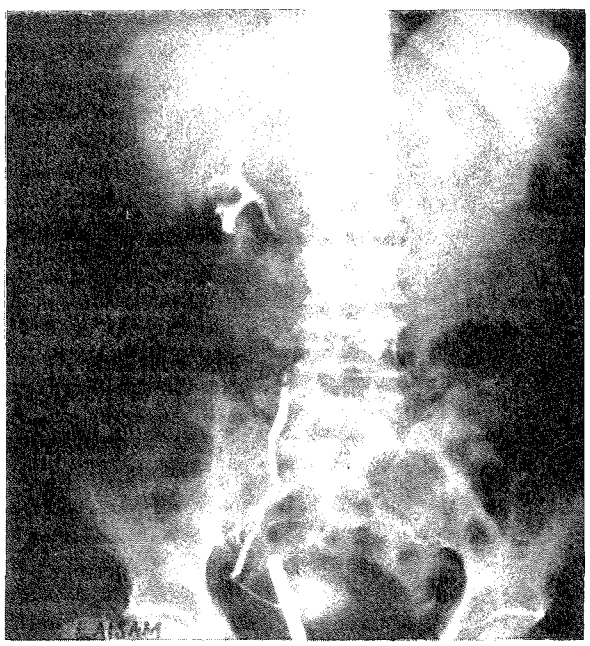

Fig. 1b Right retrograde pyelogram: Blunting of the papillae are noted, though not as severe as on the left side.

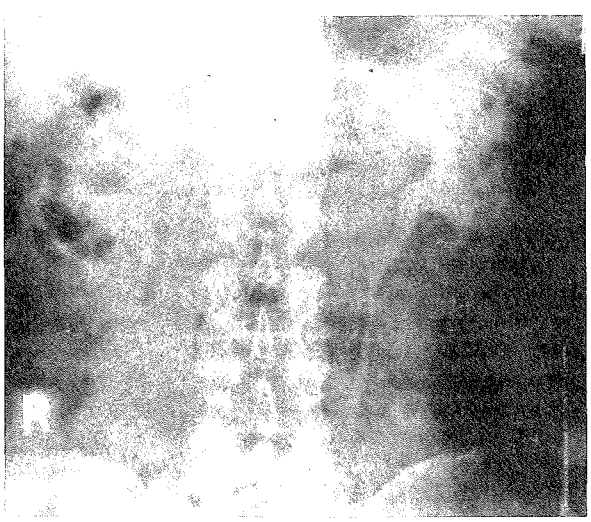

Fig. 2 IVU: Pre-contrast film shows faint pyelogram on both sides. The papillae in both kidneys show evidence of papillary necrosis.

Fig. 3 IVU: The tomograms show irregularity and amputation of the papillae on both sides. In addition, pooling of contrast in the necrotic papillae are noted in the left mid-polar calyces.

TABLE I

CLINICAL DETAILS OF PATIENTS STUDIED, WITH TOTAL QUANTITIES OF DRUGS CONSUMED

Case No.	Age	Sex	Race	Diagnosis	Analgesic		Past Urinary Inf.	Gout	Blood Pressure	Gastro Int. Sx	Neuro Psychiatric Sx	Premature Aging	IHD	Abuse of other drugs	Reason for Analgesic Abuse
					Paracetamol (gm)	APC (gm)									
1	32	F	I	HT, CRF migraine	5720	–	+	–	150/110	–	anxiety depression	–	–	Agarol	migraine
2	55	M	M	HT	3900	–	–	–	170/110	–	–	–	–	–	headache
3	61	M	M	gouty arthritis	4380	–	–	+	110/80	+	–	–	+	cig.	gouty arthritis
4	64	M	M	HT renal calculi	1040	–	–	–	140/90	–	–	–	+	–	backache
5	32	M	I	CRF, UTI	–	13,600 kaki tiga	+	–	140/100	–	depression suicidal attempt	–	–	–	headache
6	34	M	C	HT headache	–	590 harimau	–	–	200/130	+	anxiety, inferiority complex	–	–	cig.	headache
7	73	F	C	peptic ulcer rh. arthritis	–	2190	–	–	120/70	+	–	–	–	cig.	rh. arthritis
8	64	M	M	GI bleeding gouty arthritis	occ.	670 harimau	–	+	120/80	+	–	–	–	cig.	headache
9	63	M	C	gouty arthritis	10,950	18,380 harimau	–	+	140/100	–	–	–	–	cig.	gouty arthritis
10	41	M	M	asymptomatic proteinuria	Denies	analgesic intake	–	–	160/110	–	–	–	–	cig.	–
11	54	M	C	CRF, HT, Anaemia osteoarthritis	Denies	analgesic intake	–	–	140/90	–	–	–	–	cig.	–
12	54	M	C	CRF, HT		3860	–	–	140/95	–	–	–	–	–	rh. arthritis backache

HT – hypertension

UTI – urinary tract infection

CRF – chronic renal failure

IHD – ischaemic heart disease

TABLE II
RESULTS OF THE RENAL FUNCTION TESTS

Case No	HB (g/100ml)	Urea (mmol/l)	Creatinine (umol/l)	Uric Acid (umol/l)	Urine Protein g/24hr	Ammonium Chloride test
1	8.6	12.1	225	476	1.38	N.D.*
2	16.6	13.3	328	592	N.D.	N.D.
3	13.0	16.0	160	885	N.D.	+
4	14.0	3.8	128	544	N.D.	+
5	10.5	8.2	353	483	0.17	N.D.
6	15.4	13.8	345	500	0.20	+
7	8.6	20.9	183	383	N.D.	N.D.
8	8.7	10.8	210	700	2.7	+
9	8.4	29.6	312	665	N.D.	N.D.
10	15.8	3.6	92	342	N.D.	N.D.
11	14.9	21.8	284	714	N.D.	N.D.
12	10.2	102.3	1278	1250	N.D.	N.D.

* N.D. — Not done

Clinical details and total quantities of analgesics consumed are shown in Table I. Results of renal function tests are shown in Table II.

DISCUSSION

Twelve cases with radiological evidence of renal papillary necrosis have been documented. Seven patients had consumed more than 2 kg of analgesic, an amount sufficient to meet the criteria of analgesic abuse. Two patients denied analgesic abuse and three patients had consumed less than 2 kg of analgesics. This however does not exclude the diagnosis of AN as it is well known that many patients with AN will deny analgesic abuse. [2]

Four patients with AN had been abusing paracetamol, two patients had been abusing Chap Harimau and Chap Kaki Tiga and two patients had been abusing multiple combination of analgesics. The role of paracetamol in causing AN is discussed elsewhere.

AN occurs five to six times more frequently in females than in males and rarely occurs under the age of 30 years. [3] This study demonstrates a preponderance of males with the male to female ratio being 5 to 1.

Contrary to the experience in Western countries, [3] three cases (25%) of AN occurred between the ages of 32 and 34. It is hence observed that in our population AN is not uncommon in the younger age groups.

In view of the small number of cases involved, statistical analysis was not performed to compare the incidence of AN in the different races. However the figures do suggest that AN occurs equally in all the races, there being no racial preponderance (Malays 5, Chinese 5, Indians 2).

Gastrointestinal manifestations occur in more than half the patients and peptic ulceration particularly a giant ulcer has been reported in up to 35% of patients. [4,7] In our study, 33% of the patients had symptoms of peptic ulceration.

Approximately 60 to 90% of AN patients have anaemia commonly due to gastrointestinal blood-loss and chronic renal failure. [8] Anaemia was present in 50% of the patients in our study.

Ischaemic heart disease occurs in over a third of the patients with AN. [9,10] It appears to be related to the duration of disease, degree of renal insufficiency and severity of hypertension and is commonly associated with generalised atherosclerosis. Ischaemic heart disease occurred in one sixth of our patients with AN.

Patients with AN appear prematurely aged and this may due to the prominent presence of wear-and-tear pigments. [3,11] None of our patients with AN appeared prematurely aged.

Psychological and psychiatric manifestations are common in patients who abuse analgesics. They often have other addictive habits like purgative abuse, smoking, alcoholism and the use of psychotropic drugs and sleeping tablets. They also have personality traits and inadequacies such as

introversion and neuroticism. [8] 25% of our patients with AN had psychiatric manifestations such as anxiety neurosis, depression, suicidal tendency and inadequate personality. One patient had been abusing laxatives and six patients (50%) are chronic smokers. None of our AN patients had been abusing alcohol, psychotrophic drugs or sleeping tablets.

The presence of proteinuria in patients with AN is a bad prognostic sign and is associated with glomerular changes such as focal and segmental areas of sclerosis and hyalinosis. [12] Two of our patients (Case 1 and 8) had proteinuria of more than 1gm per 24 hours. Case 1 has now reached end stage renal failure and is currently being prepared for haemodialysis.

The reasons for analgesic abuse in the patients who admitted abusing analgesic are headache (50%), gouty arthritis (20%), rheumatoid arthritis (20%) and chronic backache (10%). It is important therefore, to check the renal profiles regularly and where indicated to do an IVU in patients who have been abusing analgesics regularly especially those with headache and arthritis.

It was initially considered especially in the United Kingdom and Europe that the major cause for AN was phenacetin and not aspirin. [13] One of the reasons advanced for this was that AN was rare in patients with rheumatoid arthritis who have been consuming aspirin. Post-mortem studies done on patients with rheumatoid arthritis show an incidence of renal papillary necrosis varying from 7.8% to 57.1%. [14] Terminal renal failure is however rare in patients with rheumatoid arthritis and the reasons have been reviewed by Nanra *et al.* [14] Many of the patients with arthritis in Malaysia consume excessive amounts of Chap Harimau and Chap Kaki Tiga which are compound analgesics containing aspirin, phenacetin and caffeine and the possibility of AN occurring in these patients should be borne in mind.

REFERENCES

[1] Prescott L F. Analgesic nephropathy — The international experience. *Aust NZ Med J* 1976; **6:** 44-48.

[2] Murray R M. The origins of analgesic nephropathy. *Brit J Psychiat* 1973; **1:** 99-106.

[3] Nanra RS. Analgesic nephropathy. *Med J Aust* 1976; **1:** 745-748.

[4] Dawborn J K, Fairley K F, Kincaid-Smith P, King W E. The association of peptic ulceration, chronic renal disease and analgesic abuse. *J Med* 1966; **35:** 69-83.

[5] Olafsson O, Gudmundsson K R, Brekkan A. Migraine, gastritis and renal papillary necrosis: A syndrome in chronic non-obstructive pyelonephritis. *Acta Med Scand* 1966; **179:** 121-128.

[6] Duggan J M. Aspirin in chronic gastric ulcer: An Australian experience. *Gut* 1976; **16:** 378-184.

[7] Floate D A, Duggan J M. Hour-glass stomach: An explanation. *Med J Aust* 1976: 674-676.

[8] Nanra R S, Stuart-Taylor J, de Leon A H, White K H. Analgesic nephropathy: Etiology, clinical syndrome, and clinico-pathologic correlations in Australia. *Kidney International* 1978; **13:** 79-92.

[9] Duggan J M. The analgesic syndrome. *Aust N Z J Med* 1974; **4:** 365-372.

[10] Krishnaswamy S, Wallace D C, Nanra R S. Ischaemic heart disease in analgesic nephropathy. *Aust NZ Med J* 1974; **4:** 426.

[11] Gault M H, Rudwal T C, Engles W D, Dosseter J B. Syndrome associated with the abuse of analgesics. *Ann Intern Med* 1968; **68:** 906-925.

[12] Mehta A, White K H, Nanra R S. Significance of proteinuria in analgesic nephropathy. *Aust NZ J Med* 1977; **7:** 200-201.

[13] Abel J A. Analgesic nephropathy - A review of the literature, 1967-1970. *Clin Pharmacol Ther* 1971; **12:** 583-598.

[14] Nanra R S, Kincaid-Smith P. Renal Papillary necrosis in rheumatoid arthritis. *Med J Aust* 1975; **1:** 194-197.