Clinical Problems

Analgesic Nephropathy

D. P. E. KINGSLEY, B. GOLDBERG, C. ABRAHAMS, A. J. MEYERS, K. I. FURMAN, I. COHEN

British Medical Journal, 1972, 4, 656-659

Summary

Sixty-six patients were seen from January 1963 to December 1970 in whom a diagnosis of analgesic nephropathy was made. The ratio of women to men was 2.7:1 and women presented at an earlier age. Over 60% of patients had or developed urinary tract infection and over one-third presented with serum urea levels over 300 mg/100 ml. Hypertension was present in 60% of patients and almost 20% had a history of peptic ulcer; hysterectomy had been done in 35% of the women. Most patients improved initially but more than half of those followed up died within five years of presentation. A direct relation was found between prognosis and the degree of functional renal impairment at presentation. Hypertension appeared to have an adverse effect on prognosis but no relation of prognosis to papillary necrosis, infection, or surgical procedures was found.

Introduction

Since the first description of renal damage associated with massive intake of analgesics containing phenacetin¹ about 2,000 to 3,000 cases have been reported. From 1951 to 1960 in the United States, Canada, Australia, and Switzerland the consumption of analgesics containing phenacetin doubled that in the preceding 10 years.²⁻⁵ The disease appears to be more common in Switzerland, Scandinavia, and Australia than in the United States, and apart from a few reports⁶⁻⁹ little has been written on the condition in South Africa. This paper records our experience of the disease in the renal unit of the Johannesburg Hospital over the period January 1963 to December 1970.

Present Series

During the eight years 940 patients were seen. Sixty-six were considered as having renal disease due to analgesic abuse—that is, 7%. Of these, 18 were male and 48 female, a ratio of 1:2.7. The ages of the women were 23-65 (mean 42 years), and of the men 33-62 (mean 50.5 years). We used three main criteria for diagnosis.

Historical.—All but two patients gave a history of heavy and prolonged consumption of analgesics. In 16 patients, seven of whom had abnormal but not typical radiological findings, the diagnosis was made on the history alone. The remaining 50 patients had radiological or histological confirmation, or both, of the diagnosis. The longest period of intake was 35 years and the largest calculated cumulative dose 25 kg of phenacetin. The shortest admitted period of intake was two years, with a total dose of about 1.3 kg.

Radiological.—The radiological appearances of an analgesic kidney may be indistinguishable from chronic pyelonephritis.¹⁰ Confirmation of the diagnosis was accepted if there was clubbing of the calices together with the "halo sign" or filling defects in the calices or renal pelvis or both—that is, evidence of papillary necrosis. Twenty-three patients had radiological evidence as well as a strong history but histological confirmation of the diagnosis was not obtained.

Histological.—In 27 patients the disease was confirmed on renal biopsy, nephrectomy, or necropsy material or histological examination of passed papillae according to the criteria of Abrahams and Levin.⁸ Of these patients 11 had both histological and radiological criteria for diagnosis.

Clinical Features

Symptoms at the initial presentation fell into three main groups—namely, those referable to the urinary tract, to the cardiovascular system, and to uraemia (Fig. 1). Seventeen

FIG. 1—Clinical features at presentation.

Departments of Nephrology and Pathology, University of Witwatersrand, South Africa

D. P. E. KINGSLEY, F.R.C.S., Urological Registrar (Present Address: Department of Radiology, Royal Postgraduate Medical School, London W12 0HS)

B. GOLDBERG, M.D., F.R.C.P., Senior Physician

C. ABRAHAMS, F.F.PATH (S.A.), M.R.C.PATH, Pathologist

A. J. MEYERS, F.C.P.(S.A.), Physician

K. I. FURMAN, B.Sc., F.R.C.P., Physician

I. COHEN, F.R.C.P., Physician

women and six men (35%) required dialysis for initial management. The monthly frequency of the initial presentations is shown in Fig. 2.

FIG. 2—Month of initial presentation.

URINARY TRACT

Infection.—Presenting symptoms suggestive of urinary tract infection occurred in 25 patients. In 13 of these a significant bacterial growth was found on urine culture, in 5 pyuria without organisms, and in 7 there were no organisms or pus cells. Seventeen patients with pus cells and a significant bacterial growth and five with a sterile pyuria did not have symptoms of urinary tract infection. Eleven patients without infection initially developed infection later, so that a total of 41 patients (62%) had an infected urinary tract at some stage of their disease. Treatment of the infection in these cases was often unsuccessful and in more than half there was either failure to eliminate the original infection or recurrence.

Haematuria.—Haematuria occurred in 22 patients (33%), being macroscopic in 13 and microscopic in 9.

Ureteric Colic.—Twenty-seven patients (41%) gave histories of one or more episodes of ureteric colic. Of these, 20 passed papillae on at least one occasion, mostly spontaneously but in six patients removal of papillae with a Dormia basket was necessary.

CARDIOVASCULAR SYSTEM

Cardiovascular symptoms were common. Twenty-five patients (38%) had clinical or radiological enlargement of the heart or fluid overload or both. In only one of these was there evidence of pre-existing heart disease.

Hypertension was present on initial admission in 21 women and 12 men (50%). In several cases this was directly related to fluid and sodium overload, but 15 women and 10 men (38%) required antihypertensive drug treatment in addition to salt and water depletion for control of the blood pressure. Hypertension was sometimes difficult to control, and in several patients it contributed to the cause of death or reason for transplantation.

URAEMIC MANIFESTATIONS

Neurological.—Drowsiness, fits, confusion, or coma occurred in 14 women and 7 men (31.8%). Of these coma was the immediate cause of admission in two women and five men. Peripheral neuropathy was evident in seven women and one man.

Gastrointestinal.—Nausea, vomiting, and anorexia not associated with peptic ulceration occurred in 34 patients (51%). As in other series^{11 12} a history of previous peptic ulceration was common, being present in 13 patients (19.7%), of whom 7 had undergone gastrectomy several years before initial presentation.

General.—Weakness and fatigue were the presenting symptoms in 26 women and 9 men (52.5%) and had lasted an average of four weeks. Excessive bruising was an initial complaint in

eight patients (12%), while polydipsia in 13 patients (19.7%) and polyuria in 20 (30%) made up the rest of the main symptoms. A history of hysterectomy was often present. No fewer than 17 women (35%) gave a history of hysterectomy on an average of four years before their initial admission. Two other patients had hysterectomies during their period of follow-up. The most frequent reason given for ingestion of analgesics was severe headache, frequently labelled as migraine but usually bearing little resemblance to it when a careful history was obtained. Forty-eight patients (73%) have this as their main reason for taking tablets. Backache in four patients, sinusitis in three, joint pains in three (one of whom had haemophilia), and chest pain after empyema in one made up the remainder of reasons. In six patients no reason was given for their self-medication and one denied taking analgesics. Although assessment of character is extremely difficult many of these patients were followed up for several years, and it is our impression that most were either depressed or anxious or had inadequate personalities. Descriptions such as "very odd," "peculiar," and "hypochondriac" were common in the case notes, and several patients had had psychiatric treatment.

Laboratory Findings

The serum urea level was normal in only four patients on admission. In all others it varied between 47 and 820 mg/100 ml. Serum creatinine levels were correspondingly raised and creatinine clearances, when done, were reduced.

Most patients presented with anaemia, usually mild, though in 11 patients the haemoglobin was less than 8 g/100 ml. The commonest anaemia was of a normochromic normocytic type. In eight patients persistent reticulocytosis suggested the presence of excessive haemolysis; in six iron deficiency was present and in one macrocytic anaemia. Sulphaemoglobin and methaemoglobin when looked for were not found.

At least moderate degrees of acidosis were almost always present. In seven patients this was severe, the serum total CO₂ content being less than 5 mEq/l. This was associated with serum urea levels of over 300 mg/100 ml. Five patients had hyperchloraemia whenever there was acidosis.

Renal osteodystrophy was detected radiologically in only one patient. A further five, however, had serum alkaline phosphatase levels persistently above 15 King-Armstrong units not attributable to liver disease, thus in 9% there was presumptive evidence of osteodystrophy. Proteinuria was a frequent finding as in other series but in all cases was mild. Levels greater than 3 g/24 hours were not encountered.

Follow-up and Prognosis

Nine patients were lost to follow-up. The remaining 57 were followed either to the present or to a renal death (see Table). The latter patients totalled 29—19 women and 10 men (51% of those followed up). Of the men 2 received kidney transplants and 8 died without transplantation having been done. Ten women received transplants, of whom two subsequently died. Two women, one of whom awaits transplantation, were put on to regular haemodialysis and seven others died without transplantation or regular dialysis. Of those who reached a renal death 7 presented in terminal renal failure and no improvement

Prognosis related to Duration of Follow-up in 57 Patients

Months of follow-up:	Immediate	<12	24	36	48	60	>60
Dead	7	10	2	3	3	3	1
Deteriorated	0	1	1	1	0	0	0
Static	0	3	5	1	2	3	2
Improved	0	2	4	2	1	0	0

in renal function was achieved. A further 10 patients reached terminal stages within the first year and another 12 after a longer period. All were frequently warned most strongly of the dangers of taking further analgesics, and so far as could be ascertained all stopped once the situation had been explained. Despite this the disease frequently progressed relentlessly, though sometimes deterioration was slow. Four patients reached end-stage renal failure four or more years after their initial presentation.

The 28 patients who were still alive without transplantation or regular haemodialysis were followed up for periods of 6 to 96 months (mean 27 months). One man and 8 women (15.8%) showed clinical and biochemical improvement. Another 4 men and 12 women (28%) with a mean follow-up of 40 months remained stable. Thus 25 out of 28 patients who were followed up and were still living maintained a satisfactory state of renal function. The remaining 3 patients from this group had deteriorated over periods of 6, 21, and 30 months. Two of them had virtually reached end-stage renal failure.

It appears from this series that with an overall mortality of 51% the disease in South Africa carries a worse prognosis than in most other countries. Part of this may be due to the number of patients initially presenting in irreversible terminal renal failure. Undoubtedly, however, in many cases the disease also appears to progress relentlessly despite reasonable management. Factors which may have influenced the course of the disease in this series were studied and subjected to statistical analysis. The patients were divided into four groups according to progression of their renal function—(1) improvement with rising creatinine clearances (9 patients); (2) stable renal function (16 patients); (3) slow deterioration (14 patients); (4) rapid deterioration within one year (18 patients).

Renal Function.—Patients were grouped into those with a serum creatinine of less than 5 mg/100 ml and those with a level of 5 mg/100 ml or more after stabilization at initial admission. Of those with creatinines less than 5 mg/100 ml 13 were in groups 1 and 2 and three were in groups 3 and 4, while of those with a level of 5 mg/100 ml or greater 12 were in groups 1 and 2 and 29 were in groups 3 and 4. Thus the more severe the renal functional impairment the worse the prognosis, although some patients improved even when there was gross renal insufficiency. These figures are statistically significant ($P < 0.01$).

Age of Presentation.—The mean age of presentation for women was 42 years and for men 50.5 years (Fig. 3). The disease was more common in older than in younger men. Among the women, although there was wider distribution of ages at presentation probably the onset of the condition at a later age does not have the same bad prognosis as it has in men. Only two of the men had serum creatinine levels below 5 mg/100 ml, while 13 of the women had levels below 5 mg/100 ml. The apparent difference in prognosis between men and women

at different ages can be accounted for by the severity of the renal functional impairment at presentation.

Hypertension.—Of those patients followed up 39 either had hypertension on presentation or developed it at a later period (14 patients in groups 1 and 2 and 25 in groups 3 and 4). Fifteen patients were normotensive throughout follow-up (9 in groups 1 and 2 and 6 in groups 3 and 4). These figures, which suggest that the development of hypertension may adversely affect prognosis, are not, however, statistically significant ($P > 0.05$).

Infection. Gault *et al.*¹² stressed the importance of infection, particularly acute pyelonephritis, in analgesic nephropathy. Rapid deterioration of renal function may occur with sloughing of most of the papillae and parenchymal contraction. In this series 37 patients with adequate follow-up developed infection at some period of their disease (15 in groups 1 and 2 and 22 in groups 3 and 4). Ten patients remained uninfected—5 in groups 1 and 2 and 5 in groups 3 and 4. Clearly, therefore, infection did not play a significant part in prognosis in this series. The prognosis was better related to the severity of renal functional impairment than to the presence or absence of infection.

Papillary Necrosis.—Papillary necrosis has been associated with infection and rapid acute deterioration of function, but there is little evidence that it has any permanent effect on renal function. Furthermore, it may be present even in the absence of radiological features or history of colic.¹³ Sometimes the papillae do not slough and are not passed. Thirty-three patients with adequate follow-up were known to have passed papillae on one or more occasions or had radiological changes of papillary necrosis. Of these, 18 were in groups 1 and 2 and 15 in groups 3 and 4; in the 24 patients without clinical papillary necrosis the figures were 7 and 17 patients respectively.

Surgery. Koutsaimanis and de Wardener¹⁴ and Dawborn *et al.*¹¹ suggested that surgical procedures may be associated with prognosis. In this series various operations were performed, and of the patients with adequate follow-up 13 had hysterectomy, 8 gastrectomy, and 3 various other major operations. In 3 of these 24 patients the surgical procedures were done during the period of follow-up, so that the state of renal function before the procedure was well documented. One of these patients had moderately impaired renal function, which was static up to the time of surgery but then deteriorated gradually over the next two years to end-stage renal failure. In the other two the mild preoperative impairment of renal function was not affected by the procedure. Nine patients had surgical procedures in the three years before their initial presentation, and of these five died. Twelve patients had surgical procedures more than three years before their initial presentation and two died. Probably the mortality was greater in those operated on closer to the time of presentation, but in no instance did rapid deterioration occur after surgery.

Discussion

Gault *et al.*¹² and Koutsaimanis and de Wardener¹⁴ laid great stress on the need to make specific inquiry into drug abuse, to persist in questioning not only the patient but also the close relatives, and to spare no effort in trying to make the diagnosis whenever the cause of renal failure is in doubt. Thus one of our patients repeatedly denied drug abuse but was subsequently found to be consuming tablets from a large bottle in her ward locker.

The condition seems to be common in Europe and Australia but relatively rare in the United States. So far it seems to have received little attention in Africa, only clinical and experimental work having come from Abrahams *et al.*⁶⁻⁹ Since the report of Abrahams and Levin in 1967⁸ many other cases have been diagnosed, and our series of 66 was drawn solely from the register of the Johannesburg Hospital. It includes 10 of the 14 cases mentioned by Abrahams and Levin.⁸ The frequency with which the diagnosis of analgesic nephropathy is being made

FIG. 3—Prognosis related to age of presentation. See text for description of groups.

here means that South Africa must be included in the increasing list of countries where analgesic abuse plays an important part in the aetiology of chronic renal failure.

The effect of climate on the aetiology of the condition is difficult to assess. Kincaid-Smith¹⁵ suggested that high climatic temperatures may predispose to dehydration and so precipitate acute renal failure. The condition is apparently more common in Queensland than in other parts of Australia and occurs more frequently in the summer months than in winter in Melbourne. By contrast the condition appears to be more common in northern than in southern Europe, where mean temperatures are considerably higher. Johannesburg is situated on the reef in the Transvaal 5,750 ft (1,750 m) above sea level and enjoys a sunny climate. Humidity is low all the year round and falls to around 10% in the winter. The winter months May to August are often without rain. By contrast the summer is a wet season, with short, heavy storms. Because of the altitude summer temperatures seldom exceed 85°F (average 74°F) (29.4°C, average 23.3°C) and in the winter average 52°F (11.1°C). The initial presentation of our patients occurred at any time of the year (Fig. 2), and this does not suggest that climatic conditions play a major part in the pathogenesis of the condition.

It is generally reported that timely withdrawal of analgesics results in clinical and biochemical improvement and that early diagnosis is life-saving.¹⁵⁻¹⁷ World figures suggest that the mortality rate in analgesic nephropathy varies between 20 and 30%.¹²⁻¹⁴⁻¹⁶ In our series 29 of the patients followed up (51%) reached end-stage renal failure. Nevertheless, of those who survived with follow-up of 6 to 96 months only three showed any deterioration. The remainder either improved or were static.

The overall prognosis of this series, therefore, was generally worse than in other reported series. Analysis of differences between those who deteriorate or improve suggest that the severity of the disease at presentation and possibly the presence of hypertension may be the most important factors in determining the outcome. The reasons why analgesic nephropathy should have a worse prognosis in South Africa than has been reported elsewhere are not apparent from this study.

References

- Spuhler, O., and Zollinger, H. U., *Zeitschrift für klinische Medizin*, 1953, 151, 1.
- Ross, P., *Medical Journal of Australia*, 1962, 2, 639.
- Shelley, J. H., *Clinical Pharmacology and Therapeutics*, 1967, 8, 427.
- Canada. Dominion Bureau of Statistics, Cat. No. 46-209 (1950-64).
- Canada. Dominion Bureau of Statistics, Cat. No. 65-007 (1946-65).
- Abrahams, C., Rubenstein, A. H., and Levin, N. W., *Nature*, 1963, 200, 695.
- Abrahams, C., Rubenstein, A. H., Levin, N. W., and Wunderlich, U., *Archives of Pathology*, 1964, 78, 222.
- Abrahams, C., and Levin, N. W., *Medical Proceedings*, 1967, 13, 501.
- Abrahams, C., and Levin, N. W., *Lancet*, 1968, 1, 645.
- Lindvall, W., *Acta Radiologica*, 1960, Suppl. No. 192, 112.
- Dawborn, J. K., Fairley, K. F., Kincaid-Smith, P., and King, W. E., *Quarterly Journal of Medicine*, 1966, 35, 69.
- Gault, M. H., Rudwal, T. C., Engles, W. D., and Dosseter, J. B., *Annals of Internal Medicine*, 1968, 68, 906.
- Fairley, K. F., and Kincaid-Smith, P., *British Medical Journal*, 1968, 1, 156.
- Koutsaimanis, K. G., and de Wardener, H. E., *British Medical Journal*, 1970, 4, 131.
- Kincaid-Smith, P., *Medical Journal of Australia*, 1969, 2, 1131.
- Bell, D., Kerr, D. N. S., Swinney, J., and Yeates, W. K., *British Medical Journal*, 1969, 3, 378.
- Steele, T. W., and Edwards, K. D. G., *Medical Journal of Australia*, 1971, 1, 181.

Conservative Treatment of de Quervain's Disease

JEAN M. M. MCKENZIE

British Medical Journal, 1972, 4, 659-660

Summary

Thirty patients with de Quervain's disease were treated by injection of hydrocortisone acetate and lignocaine. A 93% incidence of complete relief of symptoms was obtained after 18 months. It is recommended that this is the treatment of choice before resorting to surgery.

Introduction

The treatment of stenosing vaginitis of the common synovial sheath of the extensor pollicis brevis and abductor pollicis longus (de Quervain's disease) has often been described. Most authors advocate surgery as the treatment of choice.¹⁻⁴ Woods⁵ went so far as to state that once the diagnosis is made immediate operation should be performed. He also stated that conservative treatment only lessens the symptoms for a brief period and has no lasting value. Other workers¹ believe that all forms of treatment except surgery are largely ineffective.

The purpose of this paper is to prove that injection of hydrocortisone acetate into the sheath using the correct technique produces dramatic and lasting relief of symptoms and that surgery is rarely necessary.

Present Series

Between 1966 and 1968 30 cases of de Quervain's disease were seen and treated in the department of physical medicine. The patients (25 women, 5 men) were aged between 25 and 74 years. Symptoms varied from moderately severe pain, worse on movement, to excruciating pain causing severe disability. Duration of symptoms varied from five weeks to nine months. On examination the classical signs as described by de Quervain⁶ were found. In eight cases there was a visible or palpable swelling. The presence of a swelling was not related to the duration of symptoms.

TREATMENT

Once the diagnosis was made all patients received an immediate injection into the synovial sheath of 25 mg hydrocortisone acetate and 1 ml of 2% lignocaine mixed in the same syringe. The advantages of using a rapidly acting local anaesthetic are twofold. Symptoms are relieved almost immediately and the efficacy and accuracy of the injection can be assessed.

All patients were seen two weeks after the initial injection. If relief of symptoms was not complete or any pain or tenderness could be elicited a second injection was given. These patients were again seen after two weeks. All patients were reviewed 12 weeks after injection.

TECHNIQUE

The forearm is placed in midpronation with the thumb-nail facing upwards. A small pad is placed under the wrist to produce

Peterborough District Hospital, Peterborough PE3 6DA

JEAN M. M. MCKENZIE, F.R.C.S., D.PHYS.MED., Consultant Physician in Physical Medicine and Rheumatology