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Review article

Tropical nephropathy - an overview

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It is generally accepted that the spectrum of renal disease in the tropics is essentially the same as in the temperate environment, but the priority determinants, natural history and factors in aetiopathogenesis do vary, even as between different parts of the tropics [1,2]. These observations are based largely on data drawn from specialised tertiary health care institutions and may not be a true reflection of the pattern in the field at large. Nevertheless, in any overview of tropical nephrology, rural or urban, young or old subjects, community or individual care, three main areas, somewhat interrelated, can be identified:

- Acute renal failure
- Glomerular disease
- Chronic renal failure

Acute renal failure (ARF)

ARF can be defined as an abrupt deterioration of renal function, usually associated with decrease in urine flow to less than 400 ml/24 hr. and subsequently with retention of water, hydrogen and potassium ions and nitrogenous waste products. Below is the list of the various causes of acute renal failure in the tropics

The commonest cause is acute tubular necrosis (ATN) precipitated by infection, bleeding, fluid loss, haemolysis, nephrotoxins, shock and disseminated intravascular coagulation (DIC). These causes are often interrelated, with severe infection/bleeding or fluid loss leading to shock. In the African setting the infections to be specially wary of are septic abortion, severe gastroenteritis, enteric fever and pyomyositis [3,4]. Contrary to impressions widely carried in older literature, blackwater fever is very seldom associated with acute oliguric renal failure in adult indigenous residents in holoendemic malarious areas, if these communities are left undisturbed in their endemic environment [5]. Plasmodium infection may excite a hypersensitive response with resulting haemolysis.

With regard to haemorrhage, special mention must be made of the carnage of road traffic accidents in many developing countries. With over 10,000 killed or severely injured annually on Nigerian roads, the risk to life and limb is considerable. ATN resulting from massive intravascular haemolysis may be due to G6PD deficiency [6], sickle cell disease, enteric fever or snake venom with the last two sometimes also leading to disseminated intravascular coagulation.

Acute Renal Failure in the Tropics

1. Acute tubular necrosis:
   Septicaemia (e.g. Septic abortion)
   Haemorrhage (e.g. Trauma, Post-operative, Gastrointestinal)
   Excessive fluid loss (e.g. Gastroenteritis)
   Haemolysis
   Nephrotoxins
   Crush syndrome
   Disseminated intravascular coagulation
2. Acute glomerulonephritis
3. Obstructive uropathy
4. Acute interstitial nephritis

Apart from the above, acute renal failure has been precipitated by certain forms of traditional medicament (e.g. cow's urine in the "treatment" of childhood convulsions or camphor-containing concoctions in adult fever), misuse of chemical agents (lysol, mercuric chloride) and renal papillary necrosis from sickle-cell haemoglobinopathy (notably AS). Less common causes include diabetes mellitus, acute oliguric glomerulonephritis or fulminating pyelonephritis with multiple abscesses following obstructive uropathy.

In most of these conditions, the circumstances of the case will usually make the diagnosis clear. Quite often the symptoms of the primary disease overshadow the conventional descriptions of oliguria, azotaemia, hyperkalaemia and acidosis. When the history is unreliable or the patient is too ill to volunteer a coherent account it becomes difficult to distinguish between acute and acute-on-chronic renal failure. In the latter condition the following features are useful in differentiation.

(i) Normochromic normocytic anaemia.
(ii) Reduced kidney size (long axis of 10 cm or less) on a plain abdominal film, ultrasound or neprotomogram
(iii) Detection of any stigmata of chronic renal failure -- nocturia, polyuria, pruritus, band keratopathy, hypertensive retinopathy, peripheral neuropathy and secondary hyperparathyroidism as shown by subperiosteal erosions of the phalanges or evidence of renal osteodystrophy.

While this distinction is being pursued, it is important to define other areas of systemic involvement and institute a regime of management to deal with the rapidly evolving consequences of acute renal insufficiency. A careful urinalysis, blood chemistry, serology, further radiography (e.g. radionuclide scan), cystoscopy, ureteral catheterisation and even a renal biopsy may be necessary to assess the role of several aetiologic factors.

Measures to deal with the rapidly evolving renal impairment depend on the phase the patient is in -- prophylaxis, oliguric or recovery, and these differ in no important respects from standard management in the temperate environment.

Glomerular disease

Glomerulonephritis (GMN) is probably the most exciting aspect of tropical nephrology today [7]. Its aetiopathogenetic cost implications are modest compared with the management of endstage renal disease, yet its potential for prevention is immense. Glomerulonephritis may present with an acute nephritic picture with oedema, haematuria, oliguria and hypertension. It may also present with the nephrotic syndrome or with renal failure from a hitherto undetected chronic glomerulonephritis.

Acute post-streptococcal GMN has been linked in many parts of Africa with impetigo and with pyoderma that follows secondary infection of scabies [8]. Although Group A streptococci have been isolated from skin lesions, M-serotypes 49 and 55, normally associated with nephritis, were by no means predominant. In the paediatric setting it is easy to mistake acute GMN in a malnourished child for the nephrotic syndrome because of the co-existence of hypoalbuminaemic oedema. While most patients with AGN acute glomerulonephritis recover completely, a few progress and many present with the nephrotic syndrome, or chronic renal failure and hypertension.

It has been known for many years that the nephrotic syndrome (NS) is 10 to 100 times more common in East and West Africa [9,10] than in western Europe, and occurs more frequently in older children than in young adults. In most of Africa it often pursues a chronic relentless course, being poorly responsive to steroids, anti-malarials or immunosuppressive agents. In adults it may remain stable for many years with symptomatic treatment until hypertension supervenes when the patient then deteriorates dramatically.

Renal biopsy studies show the relative rarity of "minimal change" glomerular lesions in contrast to temperate environments. Focal and segmental changes are more common in childhood NS in the tropics. Epidemiologic, immunopathologic and histologic studies suggest that *P.malariae* is an important cause of the NS in children and adults in tropical Africa [11]. It is thought to lead to damage of the glomerular basement membrane by antigen-antibody complexes. Coarse granular immuno-fluorescent deposits containing IgG and C_3 have been demonstrated and circulating complement in the form of macromolecular C_3 aggregates were found in the sera of these patients. Other features include raised serum IgM, lowered IgG, raised titre of antimalarial antibody, elevated serum C_3 and C_4 and low titres of an adherence immune inhibition factor.

Histologic descriptions of renal biopsy samples in quartan malaria nephropathy was varied considerably between:

(a) Extensive mesangial sclerosis and flexiform thickening of the sub-endothelial areas of the glomerular capillary wall with small lacunae scattered throughout the basement membrane.
(b) Segmental or diffuse capillary wall thickening and sclerosis often producing a honeycomb appearance.
(c) Localised thickening of the capillary wall with segmental sclerosis of about a third of all the glomerular population.

The essential abnormality on electron-microscopy (EM) is thickening of the capillary basement membrane with the appearance of electron-dense deposits suggestive of immune-complexes, immunoglobulins and C_3. It must be stressed however that similar histologic and EM changes have been described in Senegalese children without strong evidence of malarial aetiology [12].

Immuno-fluorescence appearances in malarial nephropathy fall into three groups:
(i) Coarse medium-size granular deposits distributed along the capillary walls.
(ii) A diffuse pattern of very fine deposits evenly distributed along the vessels walls.
(iii) A mixture of granular and diffuse deposits.

The prognosis of quartan malarial nephropathy is generally poor. Spontaneous remission is rare and there are no lasting benefits with the use of anti-malarials or steroids.

Schistosomal GMN has also been recognised in recent years [13]. Studies in Brazil and Egypt have shown that patients with *S. mansoni* infection sometimes present with an NS-like picture, and renal biopsy reveals a membranous or membrano-proliferative lesion with immunoglobulins in the basement membrane. Those patients with *S. mansoni* are susceptible to salmonella infection and in such situations the components of complement may be readily activated.

Nephritis has also been reported, but less extensively so, in *S. haematobium* infection (Egypt, French-speaking W. Africa). It is possible that in these infections, soluble antigens are released from the adult worms in the tissue leading to soluble immune-complex GMN. Other forms of parasitic infestation in which glomerular injury has been manifest through the deposition of immune-complexes, or the detection of filarial antigen in such complexes include filariasis (*O. volvulus*, loasis [15] and toxoplasmosis [16]).

Leprosy (lepromatous or borderline) may also lead to histologic changes compatible with GMN [17] or amyloidosis. In lepromatous leprosy, circulating soluble immune complexes have been identified with linear IgG, IgM and granular C_3 deposits in the glomerular basement membrane.

Viral diseases are also well recognised as causes of tropical nephropathy [18,19]. Glomerular lesions have been described in Burkitts lymphoma, mumps, varicella, measles and dengue fever, but hepatitis B virus (HBV) presents a grave public health problem in the tropical setting, where HBV antigenaemia exceeds 10% among blood donors. In these areas there is a high carrier rate of the surface antigen HBsAg, as the preference of parenteral to oral drug administration is commonplace, so is the use of sterilisable as opposed to disposable needles and syringes. The histologic appearances in viral nephropathy are those of membranous or membrano-proliferative GMN, with occasional demonstration of the virus antigen in the immune-complex deposits on the glomerular lesions. The occurrence of multiple parasitic and sometimes viral infections in the same subject makes it difficult to attribute specific histologic changes to aetiological agents.

The use of skin-lightening creams containing aminomercuric chloride was in vogue in parts of E. and W. Africa some years ago [20]. This has led to proteinuria, and renal biopsy showed evidence of membrano-proliferative lesions which resolved on discontinuing the offending cream.

Chronic renal failure

This can follow acute renal failure of any aetiology but undoubtedly the two commonest causes of insidious impairment of renal function in the tropics are glomerulonephritis and pyelonephritis, the former being far commoner and often featuring as the terminal phase of the NS [21]. Less frequent associations include polycystic and duplex kidneys, hydronephrosis from obstructive uropathy, renal artery stenosis, collagen disorders, renal amyloidosis [22], diabetes mellitus, hereditary conditions and analgesic abuse. Some of the foregoing conditions can lead to hypertension, which further compromises renal function.

Infection of the bladder and urinary tract by *Schistosoma haematobium* is endemic in many tropical countries. Gross changes occur with bladder calcification, fibrosis, consequent hydronephrosis, chronic pyelonephritis and renal atrophy. The natural history of schistosomal renal disease

in populations in which there is a high prevalence of the disease in childhood is uncertain, and prognosis is variable. Indeed, many adults in endemic areas seem eventually to escape the terminal consequences of an infection so overwhelming in childhood.

Advanced kidney disease has been reported in *S. mansoni*, and more recently in *S. japonicum* infection in the Philippines, but this association has not been so clearly demonstrated in either human or experimental *S. haematobium* infection (although proteinuria has been noted as being unusually common in Egyptian villages with a high prevalence of *S. haematobium*).

A notable feature of chronic renal failure (CRF) in adolescents and adults in Africa is the association of oliguria and azotaemia with severe hypertension. Major challenges in CRF in the tropics relate to definitive diagnosis and realistic management.

Problems in diagnosis

It is important to distinguish at an early stage between acute renal failure and terminal acute-on-chronic failure, particularly in circumstances in which the antecedent history is unhelpful. Anaemia and skin pigmentation, so valuable in suggesting chronicity, are unreliable pointers to CRF in the black populations of the tropics. Renal imaging is perhaps the best recourse, and ultrasonography is now widely used to determine kidney size. In these situations bilateral contracted kidneys almost invariably indicate chronic irreversible renal failure. Even when such shrunken kidneys are confirmed on radiology it often proves difficult to unravel its aetiopathogenesis (GMN, pyelonephritis, hypertension or obstructive uropathy).

Problems in management

The care of patients in CRF in the tropics has been bedevilled by the nagging question of choosing between the clinically possible and the economically practicable. Peritoneal dialysis is more useful in acute reversible renal failure, and is considerably cheaper and simpler than haemodialysis in chronic renal failure where its major drawback is the complication of peritonitis. Chronic maintenance haemodialysis with renal replacement therapy (RRT) are both resource and manpower intensive. It would, for instance, be foolhardy to attempt to compete with more developed nations in the area of RRT, the outlay on which, in some countries of the western world exceeds the total health budget in many parts of the developing world. Yet these procedures can be justified on the basis of the depressing number of young adults that perish every week from what is a potentially treatable condition. The answer lies in steering a middle course in limiting such facilities to one or two national or regional centres. Continuous ambulatory peritoneal dialysis (CAPD) has a definite place because of its relative ease and more modest budgetary outlay. Patients will need to be carefully selected as infection is a common complication in the often insanitary conditions of a tropical environment.

Nevertheless, the patient with CRF in the tropical setting need not be abandoned in despair as certain conservative measures do substantially prolong life and relieve terminal suffering. One of such is the diet. The staple food in most of the tropical world is carbohydrate and because of a low-protein intake, a rise in blood urea is a late indication of advanced renal disease. The traditional low-protein, high carbohydrate feature of the tropical diet thus constitutes a providential palliative. These diets have the added advantage of producing less acid than a meat-containing diet, and the urine is frequently alkaline. All these probably relate to the apparent rarity of renal osteodystrophy in the tropical millieu.

Apart from protein, one other important aspect of management is the judicious restriction of sodium intake to 25-35 meq/day, with water intake between 2.0 - 3.0 litres/day.

Experience in a teaching hospital setting in the tropics suggests that approximately 20% of patients with terminal renal failure stabilise and show improvement with careful management, but 80% will not survive beyond six months without dialysis.

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