Current Practice

MEDICINE IN THE TROPICS

Nephrotic Syndrome and Chronic Renal Disease in the Tropics

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Chronic glomerulonephritis and the nephrotic syndrome are common in the tropics—much more common than in temperate countries. In the past the aetiological factors were largely unknown, though malaria had been suspected of playing some part. Post-streptococcal glomerulonephritis is seen in the tropics, but it could not account for the high incidence of the nephrotic syndrome and chronic glomerulonephritis found in practice. Recent interest in the relationship of chronic renal disease in Africa to malaria, particularly quartan malaria, has led to evidence being found to suggest that a considerable number of cases of nephritis and nephrotic syndrome associated with malaria progress to a chronic state.

Background

The pattern of malaria is determined by the amount of transmission taking place through the year. In many parts of tropical Africa an intense transmission takes place uniformly throughout the year and a holoendemic state exists. Similar conditions exist in many other parts of the tropics.

Plasmodium falciparum is the dominant parasite in many countries, while *P. malariae* (quartan malaria) accounts for 10-30% of positive cases. In Africa it is comparatively uncommon to find *P. malariae* in adults as a cause of clinical malaria. Infection with malaria starts during the first or second year of life and reaches a peak around the age of 5 to 7 years. It is responsible for much infant mortality and morbidity. Circulating immunoglobulins show a progressive increase with malaria infection, and these account for most of the increase in gammaglobulins found in exposed subjects in the tropics. Despite this rise a light symptomless parasitaemia persists in 6-10% of immune adults. This parasitaemia is usually due to *P. falciparum*.

Nephrotic Syndrome and Malaria

A sixty- to ninety-fold increase in the incidence of the nephrotic syndrome has been reported in the tropics,¹ and this appears to be confined to malarious areas. A decline from this order of incidence has also been reported after eradication of malaria.^{2,3} Peak malaria infection has also been found to coincide with the highest incidence of clinical nephrotic syndrome in children.^{4,5}

In clinical practice over 90% of children suffering from the nephrotic syndrome show a malaria parasitaemia. A lower but significantly increased percentage of adult cases show malaria parasites in a similar way. This increase is selective for *P. malariae*. Parasitaemia is often very light and is probably

intermittent, so its discovery requires a very diligent search. Antimalarial drugs must not be given if this search is to be successful.

There is an increase in malaria antibodies in cases of the nephrotic syndrome associated with quartan malaria. This occurs in spite of considerable losses of malaria antibodies in the urine.⁶ It is curious that this should be so, because these patients show an increased incidence of malaria parasitaemia. This observation may well be explained by Dixon's antigen-excess theory,⁷ which postulates that in immunological states where there is a slight excess of antigen over antibody antigen-antibody complexes may be found in active circulation. These complexes are capable of damaging a target organ. Evidence is now accumulating to show that this is probably true.⁸ Immunoglobulin complexes have also been demonstrated in the glomeruli of both adult and childhood cases, suggesting that the disease is probably immunologically determined. It is estimated that over three-quarters of all the cases of the nephrotic syndrome seen in the tropics are due to this cause.

Clinical Presentation

The initial clinical expression of renal involvement in quartan malaria is by the nephrotic syndrome.¹ This is true of all cases reported in the literature in both clinical and experimental work.

The classical nephrotic syndrome is reproduced: massive oedema, proteinuria, hypoproteinaemia, and hypercholesterolaemia. The oedema is usually severe and is gross in about a third of the cases. In these submandibular oedema may produce an appearance of neck retraction and the swollen eyelids may close the eyes completely. Ascites may be present in over 70% of cases, and is often very severe. This picture is particularly striking in children.

The course of the illness is swift, from a rapid onset to a severe state of oedematous swelling. Hypoproteinaemia is often very severe and the underlying cachexia may be considerable.

Additional features of azotaemia, hypertension, and haematuria may be present in the child, when the condition may best be described as "acute nephritis with the nephrotic syndrome." While this is not unknown in post-streptococcal glomerulonephritis it is particularly suggestive of quartan malarial nephrosis in the tropics. In the adult the combined picture is the rule rather than the exception. This makes it possible sometimes to predict the histological appearances of the glomeruli.⁵ The evidence so far available suggests that there is a direct link between the high incidence of tropical nephrotic syndrome and the frequency of chronic nephritis in this area, and indeed at the renal clinic at Mulago Hospital cases have been observed to pass from the nephrotic stage to that of chronic renal failure.

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Differential Diagnosis

The diagnosis is usually obvious at first sight, but it may on occasions be confused with protein-calorie malnutrition, which is a common disease in children and one which often presents with severe oedema and ascites.

Sickle-cell disease may also present with considerable swelling of the hands and feet in children and may be clinically confused with the nephrotic syndrome. Congestive cardiac failure may also cause diagnostic difficulties. In all these conditions the presence of heavy proteinuria will serve to separate cases of the nephrotic syndrome.

In the adult cardiac failure (particularly of the right ventricular variety), nutritional oedema, liver cirrhosis, the malabsorption syndrome, and severe hookworm anaemia are the most likely diseases to be confused with the nephrotic syndrome. In the latter four urine examination for protein quickly excludes the nephrotic syndrome, while in the former full cardiological investigations may be necessary. Proteinuria in heart failure, however, is rarely very heavy.

It is generally advisable to perform estimations on 24-hour urine collections for an accurate determination of daily protein loss. Figures above 7 g. in 24 hours are suggestive of the nephrotic syndrome, but the severity of proteinuria differs from day to day and twice-weekly estimations are often necessary to ascertain its severity. More usually one gets figures between 10 and 20 g. in 24 hours. Esbach's method may be used, but this tends to underestimate the severity of proteinuria and the sulphosalicylic acid method using proteinometer standards is preferable.

Biochemical Investigations

Biochemical tests can be of considerable value in the confirmation of a diagnosis of the nephrotic syndrome. Hypertension often occurs and the resulting heart failure may mask the true diagnosis. Serum protein electrophoresis and the estimation of serum cholesterol may therefore offer considerable help.

Hypoalbuminaemia is invariably present and figures of 1 g./100 ml. or less are not infrequent. The serum cholesterol is usually raised and is often a useful confirmatory test of the nephrotic state. With a low cholesterol level in the native population (150 mg./100 ml.) a rise to over 200 mg. (average 485 mg.) is a useful aid to diagnosis. A progressive increase in serum cholesterol level is a useful indication of continued activity of the nephrotic state.

Electrophoresis of plasma proteins is also very useful in diagnosis, as over 90% of cases show the nephrotic pattern. This usually shows the $\alpha_2\beta$ pattern.¹

Pathology

No distinctive histological picture occurs in the kidney in the nephrotic syndrome associated with quartan malaria. In the majority of cases, however, there are definite histological abnormalities in the glomeruli. The essential change is a proliferation of endothelial or mesangial cells of the glomerular capillary tuft. This proliferation may either be generalized or confined to a few glomeruli. In some cases only parts of individual glomeruli are involved. In these latter cases the distribution is patchy. Secondary thickening of the basement membrane (sclerosis) occurs, particularly in long-standing cases. Sclerosis is also seen in healed cases either involving a whole glomerulus or only a portion of it. Chronic or progressive cases may show much scarring and distortion of renal architecture. In some cases, however, the condition lingers on for a comparatively long period of time without any change in the appearance of the glomeruli. This is particularly true in children.

Treatment

Resistance to steroids is a characteristic feature of the nephrotic syndrome associated with quartan malaria. This is true even of children with early disease and minor glomerular changes. The occasional case is found to respond, but as the distinction between the idiopathic form as seen in Europe and that associated with quartan malarial infection is as yet uncertain it is difficult to prove that such cases belong to the true malarial group. There is little doubt that the well-known lipid nephrosis encountered in Europe occurs in tropical areas, but it is impossible at present to tell how much of it is present or what form it takes. It is possible that it provides the few cases that respond to steroid therapy.

Recently Soothill and Hendrickse² reported a qualitative difference in the pattern of protein excretion in the urine and considered that this could be used to determine which cases would derive benefit from steroid therapy. They found a less selective pattern of protein excretion in the malarial group and suggested that steroids should be given to those with a more restricted pattern of protein excretion. This suggestion warrants fuller evaluation, as it could constitute an invaluable diagnostic tool.

Side-effects from steroid therapy may appear to be frequent and often severe. This form of therapy should therefore be given with care and caution.

Immunosuppressive Therapy.—Immunosuppressants appear to be of considerable value, and remissions of proteinuria can be produced in a large percentage of children. Azathioprine seems to be the best drug for this purpose. A small dose of 50 mg. daily is capable of producing a remission within eight weeks. This dosage level is practically free of toxic effects to the bone marrow. The drug is given orally in a single dose every day.

In the adults benefit is less easily assessed. All that one can say at present is that azathioprine is worth trying. A dosage schedule of 100 mg. orally once a day has very rarely been associated with side-effects. Bone marrow hypoplasia was seen in two cases and gouty arthritis in one.

Antimalarial Therapy.—No immediate benefit results from the use of antimalarial drugs, and this is true of both the 4- and 8-aminoquinolines. Long-term malaria prophylaxis, however, may be beneficial and response to steroids may then be obtained in children.

Diuretics.—Diuretics are often the only drugs that provide any benefit to the patient, particularly the adult. Oedema is often severe and troublesome and its control offers great benefit to the patient. Powerful diuretics are required for the initial dissipation of oedema. Frusemide has been found to be very useful given in doses sufficient to produce adequate diuresis. I have often used doses of 500–600 mg. parenterally twice daily for the first few days. Once diuresis is under way it is relatively easy to maintain and an oedema-free state can then be maintained with a thiazide derivative. Children also often require diuretics in the initial stages of therapy, although few need to continue with them.

A few cases are at first refractory to diuretics. The use of plasma expanders has been found very rewarding in these cases, but they should be used with caution, particularly in cases showing significant azotaemia. A considerable decline in renal function has been noticed in patients with nitrogen retention. I confine the indications of this procedure to those cases in which there is no overt evidence of renal dysfunction. The usual dosage is 50–70 ml. of dextran or Haemecel per kg. body weight infused intravenously over the period of one hour. The same dosage may need to be repeated the following day.

Potassium supplements are usually unnecessary in people on a plain diet.

Hypotensive Drugs.—Adequate diuresis is usually sufficient to reduce the blood pressure to reasonable levels. In a few

cases, however, more powerful antihypertensive drugs may be required. The diastolic pressure must not be allowed to fall below 100 mm. Hg in the erect posture and the level of blood urea should be estimated regularly.

Other Causes of the Nephrotic Syndrome

Quartan malaria is not the only cause of the nephrotic syndrome in tropical areas. The diagnoses in a careful study⁵ of 77 cases are shown in the Table. The other known causes of the nephrotic syndrome are encountered, though much less frequently. Systemic lupus erythematosus and the diabetic kidney have also been encountered, though they were not represented in the series quoted. Membranous glomerulonephritis has never been associated with quartan malarial infection and it is probable that primary thickening of the basement membrane is not produced in this disease.

Histological Diagnosis in 77 Cases with the Nephrotic Syndrome

	Renal Lesion	No. of Cases	<i>P. malariae</i> Found
1	Proliferative	27	29
	Diffuse	11	
	Focal	17	
2	Minimal	3	1
	Nil lesion	2	1*
4	Pyelonephritis	9	0
5	Membranous	3	0
6	Chronic nephritis	3	0
7	Amyloidosis	1	0
8	Renal vein thrombosis	1	0
	Henoch-Schönlein purpura	1	0

* Also had proliferative lesions.

Other Causes of Chronic Nephritis

Chronic nephritis is the graveyard of many progressive diseases of the kidney. Of the commoner ones in East Africa

chronic urinary obstruction from stricture of urethra is the most important. Numerically, however, this is second to chronic glomerulonephritis. The patient's clinical history may not readily suggest the presence of obstruction—indeed this may be deliberately concealed by the patient.

Hypertension is very common and a great deal of it is secondary to renal disease, though essential hypertension is also frequently found.

Conclusion

The high incidence of the nephrotic syndrome in the tropics appears to be related to quartan malarial infection. In children the relationship has been established beyond doubt. Among adults the situation seems to be similar, though for technical reasons it is difficult to demonstrate the scanty parasitaemias that are known to be present. The evidence so far available suggests that progression of the underlying kidney lesion eventually produces chronic renal failure and is probably responsible for the prevalence of chronic nephritis in the tropics. Resistance to steroid therapy is a characteristic feature of this form of the nephrotic syndrome, though a remission may be obtained in a small number of childhood cases.

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TODAY'S DRUGS

With the help of expert contributors we print in this section notes on drugs in current use.

Monoamine Oxidase Inhibitors

Noradrenaline (N.A.) and 5-hydroxytryptamine (5-H.T.) are two monoamines which are thought to be important in normal brain functioning, and monoamine oxidase is an enzyme which is concerned in their inactivation. In animals it has been shown that drugs such as reserpine, which decrease the brain concentrations of these amines, result in the animal behaving as if it were depressed. Increasing the brain concentrations by administering the precursor substances or by inhibiting their metabolism with a monoamine oxidase inhibitor (M.A.O.I.) results in the animal becoming excited.

This was the rationale for the use of the monoamine oxidase inhibitors in the treatment of depression, though when they were first introduced there was no evidence that the depressive illnesses seen in clinical practice were associated with a deficiency of these amines. Recently, however, evidence has been accumulating of decreased concentration of 5-H.T.^{1,2} in the brains of depressed patients.

Both 5-H.T. and N.A. are normally stored in binding sites at nerve endings, where they are inactive but readily available for release in an active form. One such deeply bound pool is situated in proximity to the enzyme monoamine oxidase but in equilibrium with the readily available pool close to the receptor site (see Fig.). Administration of an M.A.O.I. in the dosage

used in man results in a gradual inhibition of the enzyme, an accumulation of 5-H.T. and N.A. in the deeply bound pool and by equilibrium in the readily available pool, and more amine is thus available for release when necessary at the receptor site.

Simplified model of sympathetic nerve-ending, showing the various monoamine pools.

P₁=readily available pool. R=adrenergic receptor.
P₂=deeply bound pool. M.A.O.=monoamine oxidase.
F=free monoamines.

Clinical Use

Unlike the stimulant drugs, the M.A.O.I.s are non-addictive and have no effect in patients whose symptoms stem directly from a defective or inadequate personality. They benefit only patients whose depressions have an endogenous or chemical component, for instance patients with a previously good personality who become depressed out of proportion to any environ-