

A Child with the Nephrotic Syndrome Associated with Endemic Syphilis

A Case Report

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SUMMARY

A 21-month old infant with endemic syphilis who presented with nephrotic syndrome is described. Clinically, the features correlated well with those of renal disease associated with secondary syphilis. The onset of renal disease in association with syphilis after early infancy may be a valuable aid in drawing attention to the possibility of endemic syphilis.

Morphologically the features were those of an immune complex-mediated glomerulonephritis. We regard the presence of a large number of immature-looking glomeruli as a retrogressive phenomenon.

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Until recently, endemic non-venereally transmitted syphilis was well known in Europe and other countries¹ and several outbreaks occurred among children up to the beginning of this century.²

Typically, it affects small communities where there is a high incidence of positive serological tests for syphilis.³ Although persons of any age may be affected, it is generally a disease of young children.¹⁻⁵

In different parts of the world endemic syphilis is known under various local names, e.g. 'njovera' in Rhodesia, 'dichuwa' in Botswana, 'bejel' in Syria and Iraq, 'firjal' or 'latta' in certain areas of Israel and Jordan. Unfortunately, many non-syphilitic cutaneous and oropharyngeal lesions are sometimes erroneously called by these names.⁵

Today, endemic syphilis is mainly found in dry, arid parts of the world where health standards are poor.^{1,3} Overcrowding during the cold winter nights, the sharing of feeding utensils⁴ and broken skin lesions favour the transmission of *Treponema pallidum* from one person to another in a non-venereal manner.

A primary chancre is hardly even seen^{3,5} and most cases present with condylomata lata, ulcerative lesions of the mucous membranes or the other skin lesions of secondary syphilis.^{1,3} Whether the primary lesions are overlooked, are present in an unobtrusive way or are entirely absent,⁵ is not known.

Spirochaetes, in all respects similar to the organisms causing venereal syphilis, can easily be found in the mucosal and cutaneous lesions.⁴ Usually more than one person in a household is afflicted and the members have serological tests that are strongly positive for syphilis.^{3,4} The disease responds rapidly to penicillin therapy.^{3,4} Late sequelae are destructive lesions of the skin and long bones.^{3,4} Central nervous system and cardiovascular lesions are very rarely seen,^{1,3-5} and Scott and Lups⁴ quote Murray *et al.*,⁶ according to whom the lesions may remain active for a period of up to 9 years, after which cure tends to set in spontaneously. However, tertiary lesions may develop after a period of latency.³ Congenital syphilis is rare, probably as a result of immunity developed by the mothers by the time they are old enough to bear children.³

A thorough search of the literature failed to reveal any reference to renal involvement in association with endemic syphilis.

We wish to present the clinical and pathological findings in a case of the nephrotic syndrome in a child with endemic syphilis, which, we believe, is the first description of such an association.

CASE REPORT

A Coloured boy was admitted to hospital in May 1977, at the age of 1 year and 9 months. He had been born by a normal vertex delivery at full term and milestones at the age of 1 year were normal. He was the second of 3 sibs, the eldest being apparently healthy and on the third percentile for weight and height, the youngest being sickly and below the third percentile.

The patient presented with a history of diarrhoea for 1 month, during which period generalized oedema had developed. On examination he was obviously small for age, weighing 8,0 kg and well below the third percentile. His height was 78 cm, just below the third percentile. He had generalized oedema and marked papular eczema. Shotty lymph nodes were palpable and thrush was present. His blood pressure was 110/60 mmHg. Abdominal examination revealed ascites, a 2-cm enlarged liver and a spleen at the costal margin. Examination of a urine specimen revealed 3-4+ protein and 1+ blood. Special investigations revealed a haemoglobin concentration of 8,9 g/dl and a white cell count of $23 \times 10^9/l$, with a normal distribution. Total serum protein was 49 g/l, the albumin being 15 g/l. Immunodiffusion revealed a markedly elevated IgM of 3,07 g/l, but the IgA and IgG were normal. Cholesterol varied between 7,84 and 10,85 mmol/l. Liver

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function tests and electrolyte, urea and creatinine levels were essentially normal. The serum antistreptolysin O titre was 100 Todd units. The serum complement fractions were C3 64,4 mg/100 ml (normal 80 - 120 mg/100 ml) and C4 5,8 mg/100 ml (normal 30 - 50 mg/100 ml). Both the rapid plasma reagin (RPR) and VDRL tests were positive, the VDRL titre being 1:512 on two occasions. All other investigations, including LE cell, hepatitis B antigen, chest radiography, skeletal survey, intravenous pyelography and urine cultures were either negative or normal.

Open renal biopsy was performed after conservative treatment with a high protein diet, 20% salt-free human albumin infusions and diuretics. Indications for biopsy were the obvious nephrotic syndrome in a child well below the third percentile, the significantly elevated VDRL titre, the very elevated IgM (although not specific for syphilis) and the depressed C3 and C4 complement fractions.

The tissue obtained was bisected. One portion was fixed in 10% formal saline and processed for light microscopy. Sections of 2 - 3 μ m were stained with haematoxylin and eosin, periodic acid-Schiff, Masson trichrome, PAM silver and Warthin-Starry stain for spirochaetes. The second portion was fixed in glutaraldehyde and processed for electron microscopy.

On light microscopy there were approximately 50 glomeruli; 17 of these had an 'immature' appearance (Fig. 1). They were small, the epithelial cells were cuboidal and the capillary spaces poorly developed. Two of these glomeruli showed a global sclerosis. The other glomeruli showed a diffuse endocapillary proliferative picture with accentuation in the mesangial regions. There were no adhesions or crescents (Fig. 2). An occasional tubule appeared atrophic. The interstitium contained a small number of scattered lymphocytes and plasma cells, but there was no interstitial fibrosis. The extraglomerular blood vessels appeared normal. No spirochaetes were found.

Electron microscopy confirmed the above findings. In addition to the proliferation of mesangial and endothelial cells there were numerous subepithelial and a few intra-

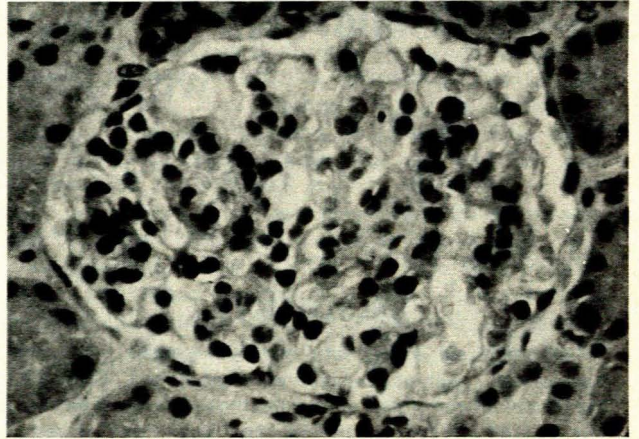


Fig. 2. Glomerulus showing proliferative changes (H and E \times 400).

membranous electron-dense deposits. The epithelial cell foot processes overlying these deposits were fused and there was microvillous transformation of the epithelial cells (Fig. 3). The overall picture was that of a diffuse, endocapillary, proliferative glomerulonephritis associated with a large proportion of 'immature' glomeruli.

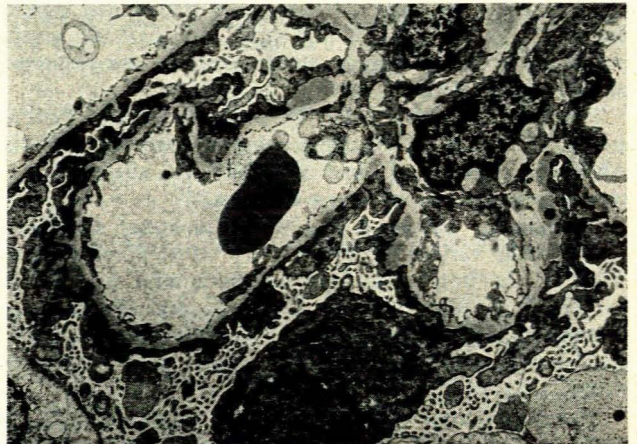


Fig. 3. Electron micrograph showing numerous subepithelial electron-dense humps, overlying foot process fusion and epithelial microvillous transformation (original \times 5900).

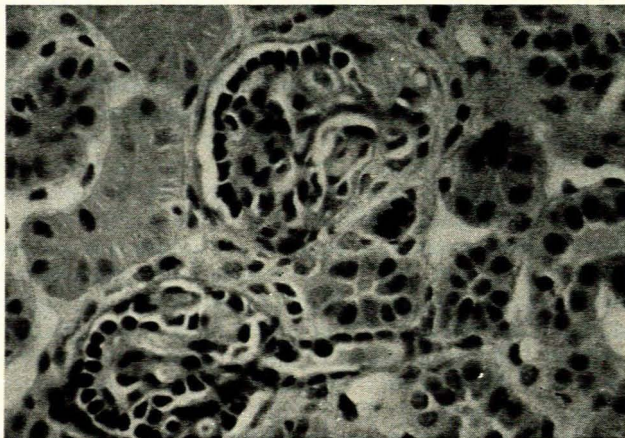


Fig. 1. Two 'immature' glomeruli. Note cuboidal appearance of cells and immature-looking tubule (H and E \times 400).

The biopsy findings were regarded as being compatible with the morphological features seen in renal involvement in congenital syphilis.

After the renal biopsy, procaine penicillin (200 000 U per day by intramuscular injection) was administered for 2 weeks. This was followed by oral penicillin. On this therapy, the child's general condition improved, and proteinuria disappeared within 3 weeks although 1+ haematuria was still present.

The child was followed up 1, 2, 5 and 9 months after discharge. He has remained in complete remission and the microhaematuria also disappeared. Total serum protein

rose to 71 g/l, the albumin being 36 g/l. The serum cholesterol fell to 3.96 mmol/l. One month after discharge the serum complement fractions had returned to normal (C3 122.8 mg/100 ml and C4 48.4 mg/100 ml). Although all serological tests for syphilis have remained positive, the VDRL titre has progressively fallen, from 1:512 to 1:8. The child has also gradually gained weight and appears to be healthy.

Comment

The response to penicillin therapy, after initial conservative treatment, appeared to substantiate the initial diagnosis of nephrotic syndrome due to syphilis. No steroid therapy was given. The diagnosis was further borne out by the virtual clinical remission within 3 weeks after initiation of therapy, the urine being protein-free at this stage, although there was still slight haematuria. The patient is still in complete remission 10 months after the disappearance of proteinuria. Furthermore, the serum complement fractions returned to normal, and there has been a continuous decline in the VDRL titre on penicillin therapy alone. Apart from the child's obvious failure to thrive, it is of interest that no other obvious stigmata of congenital syphilis were present.

A few discrepancies remained in the preliminary diagnosis of the nephrotic syndrome due to congenital syphilis: (i) the onset of the disease late in infancy was unlike that reported by others; (ii) the mother's RPR and VDRL tests were found to be negative and further serological investigations were required; (iii) the patient came from the Cedarberg area in the Clanwilliam district. This region is mountainous and dry and endemic syphilis is known to be prevalent. We therefore called on the patient and found that he lived in a well-kept 3-roomed house with his father, a farm labourer, his mother, 2 brothers and 2 male lodgers aged 5 and 9 years.

Treponema pallidum haemagglutination, RPR, VDRL, fluorescent treponemal antibody absorption and IgM absorption tests were done on all the above, as well as on other close contacts, including paternal grandparents, 2 female cousins, and the father and a female cousin of the 2 male lodgers. Apart from the initial investigation, the mother had never had any serological investigations, treatment with penicillin or evidence of syphilis. All the above tests were found to be negative, except in the 5-year-old male lodger, in whom all tests were positive, with a VDRL titre of 1:256, and in his older female cousin, with a VDRL titre of 1:8. Her IgM absorption test was negative. This woman had often acted as nursemaid to the patient. Both appeared clinically well.

DISCUSSION

There are a few accounts in the literature of renal disease associated with congenital syphilis.⁷⁻⁹ Clinically these patients present with the nephrotic syndrome,⁹⁻¹¹ occasionally with acute glomerulonephritis,⁸ or with a mixed nephrotic-nephritic picture.¹² Almost all these patients present in early infancy.^{7,8,11}

Earlier reports from the era before renal biopsy refer to clinically diagnosed cases of 'nephritis' in older children with congenital syphilis,¹³ but no histological studies were done and the symptoms could have been due to the harsh treatment used at that time, e.g. mercurial preparations. The symptoms could also have been a reflection of the late sequelae of renal disease associated with congenital syphilis, as in the more recent case reported by Timlin.¹⁴

The English literature was searched as far back as 1950 to cover all reports from well before the advent of percutaneous renal biopsy. Only one report of renal disease associated with congenital syphilis and presenting after early infancy could be found.¹⁵ We agree with the authors that syphilis was not convincingly proved to be the cause of this 9-year-old's proliferative glomerulonephritis, which in addition did not seem to respond to penicillin therapy.

The kidneys may be affected in secondary syphilis,^{16,17} as well as in the congenital form of syphilis. The most common morphological features of renal disease in congenital syphilis⁹ appear to be similar to those described in secondary syphilis.¹⁷ Although the histological findings in congenital syphilis include a membranous¹⁰ and also a mesangiocapillary⁹ form of glomerulonephritis they are most often those of a diffuse endocapillary proliferative or mesangial proliferative glomerulonephritis in both congenital^{8,9,11} and secondary syphilis.¹⁷

Our light microscopy findings correlate well with those described most commonly for congenital and also for secondary syphilis. As the clinical features of endemic syphilis are essentially those of the secondary form of this disease, one would expect the renal lesions to be similar.

Our findings of large subepithelial humps with fusion of overlying epithelial foot processes were also described in the other cases where ultrastructural studies were done.^{9,10,17,18} These humps are generally regarded as representing components of immune complexes^{19,20} and have been shown by immunofluorescence at times to contain IgG and C3^{9,17,21} and in other instances IgA and IgM.⁹ These findings and the failure to demonstrate spirochaetes in the renal biopsy specimens point to an immunologically mediated disease rather than to direct damage by spirochaetes.

Lastly, attention must be drawn to the presence of the many immature-looking glomeruli. Immature and sclerosed glomeruli unassociated with any demonstrable renal or other disease may be seen in congenital glomerulosclerosis.²²⁻²⁴ These glomeruli are most numerous in the perinatal period and disappear towards the end of the second year.²³ The cause of this condition is not known, but incomplete development and disease processes in the fetus or neonate which affect the glomeruli have been cited. In addition, immature-looking glomeruli have been described in association with hereditary nephritis,²⁵ the congenital nephrotic syndrome²⁶ and Fanconi's syndrome.²⁷ Kaschula *et al.*,⁹ McDonald *et al.*⁸ and Nabarro¹³ mention the presence of immature glomeruli in association with the renal disease of congenital syphilis.

We believe that as our patient's renal symptoms cleared up entirely on penicillin therapy, with no residual signs,

these glomeruli *per se* were of no demonstrable functional significance. As his syphilis must have been contracted after birth, the immature-looking glomeruli most probably represented retrogressive changes in previously normal glomeruli, similar to those experimentally produced by Bernstein^{28,29} in previously normal nephrons, rather than arrested development.

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Complement Consumption and Progression to Post-streptococcal Nephrotic Syndrome

A Report of Two Cases

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SUMMARY

The immunopathogenesis of the nephrotic syndrome which occurs in about 0,3% of Black children with post-streptococcal glomerulonephritis has not been clearly defined. Findings in 2 out of 582 Black children with post-streptococcal glomerulonephritis who developed nephrotic syndrome suggest that minimal activation in the blood of complement components, particularly C3, early in the nephritic process may determine progression to nephrosis. Differences reported by other workers between normocomplementaemic and hypocomplementaemic patients with

post-streptococcal glomerulonephritis support this interpretation.

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Although the nephrotic syndrome occurs during and after post-streptococcal glomerulonephritis, the frequency of this complication in developed countries varies from 4,5% to 30%.¹⁻³ In adults the nephrotic syndrome occurs more often and earlier after streptococcal glomerulonephritis than it does in children and tends to be more severe.⁴ In East African children the nephrotic syndrome has been reported to be commonly associated with post-streptococcal glomerulonephritis.⁵ Factors which are critical for the development of post-streptococcal nephrotic syndrome have not been identified.

In our experience the nephrotic syndrome is an extremely uncommon complication of a very common disease. Of 582 Black children with post-streptococcal glomerulone-

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