Membranous glomerulonephropathy in childhood

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Summary

Membranous glomerulonephropathy (MGN) in South African black and mixed race children with the nephrotic syndrome is much commoner than in First World countries. In this survey of 388 nephrotic children MGN was found in 51.9% of black and 20.9% of mixed race boys, and 25% of black and 5.6% of mixed race girls respectively, but was not present in 53 white and Asiatic nephrotic children. Aetiological or associated factors were documented in 84%: hepatitis B virus infection in 73%, congenital syphilis in 6% and systemic lupus erythematosus, d-penicillamine toxicity and Salmonella infective endocarditis in 1 case each. The prognosis depends on the cause and is much better than for adults with idiopathic MGN. After an average follow-up period of 4.5 years the overall remission rate was 78% and mean time to remission 30 months. One patient with syphilitic MGN died 15 years later; 3 patients are in mild renal failure. Corticosteroids and other immunosuppressive therapy were ineffective and may do harm.

The frequent occurrence of MGN is related to the high prevalence of predisposing infections in the affected population groups, and socio-economic rather than ethnic factors are important.

Membranous glomerulonephropathy (MGN) is a glomerular disease characterised by thickening of the glomerular capillary basement membrane due to immune complex aggregates. It leads to severe proteinuria, haematuria, with or without hypertension, and/or renal failure. MGN may be idiopathic or associated with identifiable antigens and systemic conditions such as infections, multisystem connective tissue diseases, neoplasms and drugs. First reported in childhood by Royer in 1962, MGN is relatively uncommon in this age group, and is found in no more than 1.5 - 6.8% of children investigated for severe proteinuria. 

This study was undertaken to determine the occurrence, course and possible aetiology of MGN in South African children of different ethnic origins with the nephrotic syndrome.

Patients and methods

The clinical and biochemical data, histopathological features and follow-up data of all patients up to the age of 13 years with severe proteinuria and a tissue diagnosis of MGN were reviewed. MGN was diagnosed on the basis of glomerular basement thickening due to the presence of predominantly subepithelial immune deposits. Mild mesangial proliferation and interposition were also seen at times. The majority of patients were referred from within the Cape Province and all were followed up at the Red Cross War Memorial Children’s Hospital Renal Clinic between 1969 and 1985.

The severity of the proteinuria, remission and relapse were defined by the criteria of the International Study of Kidney Disease in Children. Routine sequential assessment of renal function included urinalysis and estimation of the plasma urea, creatinine, proteins and cholesterol levels. In the majority of cases a throat swab culture, and lupus erythematosus cell preparation and/or the Crithidia test were done, antistreptolysin-O titre, antinuclear factor were measured, and syphilis and hepatitis B serology were carried out to detect possible aetiological or associated factors. Exposure to toxic substances was excluded from the history. Renal biopsy specimens obtained by percutaneous needle were examined by previously described methods.
Results

Of 388 children with the nephrotic syndrome 63 (16.2%) were found to have MGN (Table I). Fifty-one were boys (37 mixed race, i.e. Cape Coloured and Malay, and 14 black), and 12 were girls (6 mixed race and 6 black). MGN was not found in white or Asiatic children who comprised 13.7% of the nephrotic children seen. The age at clinical onset varied from 1 month to 13 years (Fig. 1) with a mean age of 74 months (median 70 months). In all 4 patients under the age of 6 months MGN was due to congenital syphilis. Black children differed significantly in their age at onset.

<table>
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<th>TABLE I. NEPHROTIC SYNDROME AND MGN</th>
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<tr>
<td>Nephrotic MGN Renal biopsies* No. % MGN</td>
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*The majority of cases not biopsied had presumed minimal-change nephropathy. MGN was not seen in white or Asiatic children.

Follow-up periods ranged from 3 months to 14.5 years, with a mean of 4.5 years. Six black patients (3 boys, 3 girls) and 2 mixed race boys were lost to follow-up after periods of 3 - 89 months (mean 23 months); 1 had asymptomatic proteinuria, the other 7 had persistent nephrotic syndrome when last seen. Six of the 14 patients with non-selective proteinuria and 5 of the 8 with selective proteinuria were in remission at the last follow-up.

The main laboratory findings are given in Table II. The glomerular filtration rate\(^{-1}\) was \(< 80 \text{ml/min}/1.73 \text{m}^2\) in 18 patients at the onset but renal failure persisted in only 2 patients, 1 of whom had congenital syphilitic nephropathy and died 15 years later. Mild biochemical renal failure developed later in 2 patients with persistent disease. Haematuria was macroscopic in 15 cases, leading to an initial erroneous diagnosis of acute postinfective glomerulonephritis.

Aetiological or associated factors were found in 53 patients (84%) (Table III). Of 53 patients tested 46 (86.7%) were sero-positive for hepatitis B surface antigen (HBsAg); 6 of these were first tested when already in remission but their clinical course had been similar to the others and they are presumed to have had HB-associated MGN. Of 39 patients tested 31 were also hepatitis B e antigen (HBeAg) positive; the 8 patients who had seroconverted to anti-HBeAg when first tested were either in remission then or soon afterwards. Mildly raised plasma alanine aminotransferase levels were detected in two-thirds of the 42 HB carriers tested, but none had clinical evidence of liver disease apart from hepatosplenomegaly. The prevalence of HBeAg in patients with glomerulonephritis other than MGN was 10.8%.

The majority (80%) remained HBs-positive throughout the course of their renal disease and even after remission, in contrast to 73% who seroconverted to anti-HBeAg shortly before or after remission. The remaining 27% had not seroconverted to anti-HBeAg as late as 2 years after remission. By the end of the study period 30 of the 40 patients followed up long-term with HB-associated MGN were in remission; 27 of these (90%) went into remission within 5 years. At the age of 2 months 1 patient had congenital syphilis and MGN but recovered fully clinically within a few months, only to present again at 3 years with HB-associated MGN. The initial biopsy of the only patient who died and who had congenital syphilitic MGN showed considerable mesangial proliferation and crescent formation; a second biopsy 6 months later showed sclerosis of more than 50% of the glomeruli. One patient had systemic lupus erythematosus (SLE) but in none of 13 other patients with raised anti-DNA antibody levels (range 11 - 94 \(\mu\)g bound/ml, mean 26 \(\mu\)g/ml) could this diagnosis be confirmed.

Forty-three (35 mixed race and 8 black) of the 55 patients (78%) followed up long-term were in remission at the last follow-up. The likelihood of remission was not affected by age, but the prognosis appeared better for mixed race children of whom 85% went into remission compared with 57% of the blacks. Time to complete remission ranged from 3 to 96 months, with a mean of 30.4 months (median 31 months); of the 43 patients who went into remission, 93% did so within 5 years (Fig. 2). All patients in
remission had normal renal function when last seen. Mean duration of the nephrotic syndrome in patients who were in remission or had improved was 20.2 months (median 17.5 months); 5 patients followed up for 2, 7, 8, 48 and 65 months still had nephrotic syndrome and 7 patients (11%) had persistent asymptomatic proteinuria at the last follow-up.

Fifteen of the earlier patients received corticosteroids for a minimum period of 4 weeks, and in 6 cases prednisone combined with cyclophosphamide was given for at least 8 weeks. In 1 case remission occurred during the combined treatment but no other patients seemed to benefit.

Discussion

MGN is relatively rare in children. Exact comparison with other studies is hampered by the varying inclusion criteria used, but the reported frequency of MGN in children with severe proteinuria is 1.5 - 6.8% compared with 19 - 30% in adults. 1-5,9,10

In this series 16.2% of 388 nephrotic children had MGN. The prevalence of MGN in South African children is thus much higher than in First-World countries and MGN is the commonest single cause of the nephrotic syndrome in South African black children. It occurs less commonly but is still frequent in mixed race children and was not seen in white and Asian children (Table I). This study confirms the findings by Adhikari et al., 11 who in a smaller series reported that MGN is the commonest nephropathy (29.8%) associated with the nephrotic syndrome in black children.

Chronic immune complex-induced MGN has been produced experimentally by repeated injections of antigenic foreign serum protein (bovine serum albumin) into rabbits; this results in the formation of small circulating immune complexes which are trapped in the glomerular basement membrane setting up an inflammatory response which can be recognised as MGN. More recent evidence suggests that cationic antigens may also lead to in situ formation of the subepithelial immune complexes. 12 In human MGN the glomerular deposits may readily be shown to contain immunoglobulin, particularly IgG, and complement fractions.

A variety of antigens and associations have been identified and in several instances the responsible antigen has been detected in the glomerular deposits. The patients in whom this occurs appear to be relatively immuno-incompetent and when unable to eliminate the antigen form nephritogenic immune complexes intermittently or persistently. Remission occurs either when the antigen is eliminated as with penicillin therapy for syphilis or when the patient’s immune response is altered.

In adults 6-12 and children 13-16 the majority of reported cases have been of unknown aetiology. In this study idiopathic MGN probably occurred even less frequently than the 16% noted, since HB virus infection was not excluded in all cases. The 84% frequency rate of secondary MGN is due to the remarkably high occurrence (73%) of HB-associated nephropathy. The latter in turn is related to the high prevalence of more than 10% of the HB carrier state in the affected population groups. 17 It is likely that this infection is acquired in many by perinatal vertical transmission, since 10 of the 16 mothers tested for HBsAg were either carriers or had previous exposure to the virus and had seroconverted to anti-HBsAg. In theory HB-associated MGN may be preventable by passive and active immunisation after birth. It is thought that the infected liver cell serves as a continual source of viral antigen material and that an incomplete immune response not only allows the HB carrier state to persist, but also favours the formation of circulating and/or in situ nephritogenic immune complexes. Several workers have been able to demonstrate HB viral antigen-antibody complexes in the circulation 6 and in glomerular immune deposits. Why the incidence of HB-associated MGN in adults is lower is unexplained but it may be due to different immunoreactivity or a lower prevalence of the carrier state.

Glomerulonephritis in the course of early congenital or acquired secondary syphilis is due to chronic treponemal immune complex deposition. The 4 cases of congenital syphilitic nephropathy are an underestimate since infants with congenital syphilis frequently have haematuria and proteinuria with hypoproteinaemia, but do not undergo biopsy as prompt recovery follows early specific treatment.

SLE is an important cause of MGN in childhood in First-World countries and glomerular disease may precede other clinical and serological evidence of SLE by several years. Despite the finding of raised anti-DNA antibodies in 41% of the 34 cases tested, SLE was documented in only 1 patient who recovered with corticosteroid therapy.

The exact pathogenetic mechanism of drug-induced MGN is unknown. The drug may act as a hapten, combine with serum and tissue proteins and modify the host immune response or alter tissue constituents, such as renal tubular epithelium, to render them antigenic. In our single case D-penicillamine, used for the dissolution of cystine stones, led to MGN during a second course of treatment several years after an uncomplicated first course. Discontinuation of the drug resulted in marked reduction of the proteinuria and resolution of the nephrotic syndrome but at the last follow-up 1 year later mild asymptomatic proteinuria was still present. Drug-induced MGN is generally reversible and does not necessarily recur on resumption of the treatment.

Socio-economic rather than ethnic factors are more important when considering the higher prevalence of predisposing infections such as HB and syphilis in the affected population groups. Since only supportive therapy is available if no remediable cause is found, a tissue diagnosis of MGN is an indication for a careful search for a treatable cause or antigen.

The incidence of MGN peaks in the 5th decade 18 but the condition may occur at any age, even in infancy. In this series 5 patients were less than 2 years old; 4 of them had congenital syphilis with glomerulonephritis. The latter in turn is related to the high prevalence of the HBsAg carrier state in males. 19 In this series the male/female ratio was a high 4.25:1.

The onset is insidious and routine screening for proteinuria will detect 21 - 57% 13,15 of the cases at the stage of asymp-
Proteinuria. Though some asymptomatic patients may remain undetected, the proteinuria almost invariably increases in severity until it becomes a symptomatic nephrotic syndrome. Proteinuria is usually non-selective but a significant number of patients have selective proteinuria, which in our study was associated with a better prognosis. Proteinuria may (and often does) fluctuate during the course of MGN, and relapses may occur after remissions of several years. Such relapses, which may be asymptomatic, do not influence the overall prognosis.

Renal failure due to nephropathy or as a result of renal hyperperfusion due to hypovolemia was found at the onset in 31% of our cases, a higher figure than in several other series but similar to Ramzy et al.'s findings. It was usually mild and transient and more often present in patients whose disease had progressed to a later histological stage.

The prognosis for MGN is cause-related. Remissions are more likely when the offending antigen is a drug or infection which may be discontinued or treated. Most reports give a better prognosis for the younger child (<5 - 6 years). In this series, if congenital nephrotic nephropathy is excluded, age had no influence on the prognosis. Patients presenting with asymptomatic proteinuria have a better prognosis than those with the nephrotic syndrome, particularly if it persists. In Third-World countries patients present later and nephrotic syndrome at the onset does not necessarily imply a poor prognosis.

A review of large paediatric series indicates a mortality or end-stage renal failure rate of 10 - 15%, which is less than half that of adults. In this series, if congenital nephrotic nephropathy is excluded, age had no influence on the prognosis. Patients presenting with asymptomatic proteinuria have a better prognosis than those with the nephrotic syndrome, particularly if it persists. In Third-World countries patients present later and nephrotic syndrome at the onset does not necessarily imply a poor prognosis.

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REFERENCES