

# Clinical review of idiopathic versus hepatitis B surface antigen related forms of membranous glomerulonephritis

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## Abstract

**Clinical features and therapeutical approaches in 10 cases of membranous glomerulonephritis (MGN) have been reviewed in an attempt to identify predictive indices of prognosis, and features distinguishing between idiopathic and hepatitis B surface antigen (HBsAg) related forms of glomerulopathy. Five of these children (age range 8–10 years) had HBsAg associated MGN and the other five (age range 12–16) lacking this antigen were defined as idiopathic MGN. The follow up was nine months to 10 years (mean 4.3 years). All had nephrotic syndrome during the course of their disease. There were no distinguishing clinical features nor any difference in the outcome between these two groups. None of the clinical findings including the presence of HBsAg, adversely affected outcome. All patients in the idiopathic group and three of the five in the HBsAg related group received immunosuppressive treatment. Overall complete remission was achieved in four of the five HBsAg associated patients and in three of the idiopathic patients plus partial remission in one of each group. Immunosuppressive treatment caused no complications, and beneficial results of the treatment particularly in the idiopathic MGN group were observed.**

Membranous glomerulonephritis (MGN) is an immunologically mediated disease of the kidney.<sup>1,2</sup> The deposition of circulating immune complexes along the epithelial side of the glomerular basement membrane is the hallmark of the disease.<sup>1,2</sup> Antigenic determinants of hepatitis B virus have been frequently implicated in the aetiology of these immune complexes and in the pathogenesis of the disease.<sup>1–5</sup> As MGN is a rare disease in childhood, reports on prognostic factors are rare both for hepatitis B virus infected patients and for idiopathic cases of MGN.<sup>6,7</sup>

We reviewed our experience at Hacettepe Children's Hospital in Turkey in order to analyse whether any of the clinical features including the presence of hepatitis B surface antigen (HBsAg) affected prognosis, and to review our therapeutic approaches to these patients. We have also aimed to define any distinguishing features between the HBsAg related and idiopathic forms of MGN.

## Patients and methods

The clinical data of 10 MGN patients, who had been diagnosed by tissue biopsy between the

years 1979 to 1990, were reviewed. Five of these patients were found to have HBsAg in their serum and they all lacked antibodies against this antigen. HBsAg tests were negative in the other five patients.

In all patients, whether HBsAg positive or not, lupus erythematosus (LE) cells, antinuclear and anti-DNA antibodies were repeatedly studied. Patients with signs of systemic lupus erythematosus or any other underlying cause have been excluded from this series. Liver function tests were within normal limits in all.

Laboratory evaluation consisted of: urinalysis, 24 hour urine protein quantification or protein to creatinine ratio in spot urine specimens, concentrations of protein, albumin, creatinine, uric acid, and electrolytes in serum, blood urea nitrogen, and liver function tests. Nephrotic syndrome was defined by the criteria of the International Study of Kidney Diseases in Children: this is protein loss of more than 40 mg/m<sup>2</sup>/hour, serum albumin concentration less than 25 g/l, and serum protein less than 60 g/l.<sup>8</sup> Urine protein was quantitated by sulfosalicylic acid in 24 hour urine samples. Partial remission was defined as absence of oedema, return of serum albumin concentration to normal values, and persistent asymptomatic proteinuria; this was a mild to moderate degree of proteinuria which was less than 2 g/24 hours.<sup>1,9</sup> Complete remission was defined as total disappearance of proteinuria while maintaining normal serum protein values. Hypertension was defined as blood pressure raised above the 95th centile for age, as previously described.<sup>10</sup> Haematuria was defined as more than five red blood cells per high power field in the urine sediment. Creatinine clearance was calculated as previously described.<sup>9</sup>

## Results

There were two girls and eight boys whose age of onset of symptoms ranged between 8 and 16 years with a mean of 11.4 years. Their follow up ranged from nine months to 10 years with a mean of 4.3 years. Percutaneous renal biopsy was performed within six months of the first symptoms of the disease in all except one patient who had complained of oedema in the last two years of follow up.

Two patients presented with hypertension, and three had hypertensive values during the course of their disease (table). Two of these patients were on corticosteroid treatment when they were noted to have high blood pressure.

Two of the patients (numbers 5 and 8) had presented only with heavy proteinuria exceeding 2 g/24 hours without any oedema, and they

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## Membranous nephropathy in 10 Turkish children

Patient No	Sex/age (years)	Blood pressure	Haematuria	HBsAg	Treatment	Outcome	Follow up (years)
1	M/8	Normal	-	+	None	Complete remission at 2.5 years	4.5
2	M/9	High	+	+	None	Complete remission at 10 years	10.0
3	M/10	High	-	+	Steroids	Complete remission in 4 weeks	1.5
4	M/9	Normal	-	+	Steroids	Partial remission in 4 weeks	0.75
5	M/10	Normal	+	+	Steroids	Partial response to treatment in 6 weeks, 8 years later spontaneous complete remission	8.0
6	M/12	High	-	-	Steroid + cyclophosphamide	Partial remission in 1 year, complete remission in 8 years	9.5
7	F/13	Normal	+	-	Steroid + cyclophosphamide	No response to treatment at 2 months, complete remission 2 years later	5.0
8	M/16	High	+	-	Steroid + cyclophosphamide, Ponticelli protocol	Complete remission after 1 year of Ponticelli protocol	4.0
9	F/12	Normal	-	-	Steroid + cyclophosphamide, Ponticelli protocol (6 months), cyclosporin	Resistant nephrotic syndrome (cyclosporin recently started)	1.0
10	M/13	High	+	-	Steroid + cyclophosphamide	Partial response in 2 months	0.8

had normal serum proteins; they subsequently developed nephrotic syndrome. The rest of the patients were nephrotic at presentation. There was a slight decline in renal function in one of the patients which subsequently returned to normal; creatinine clearance was normal in the other patients. Five of the patients had transient haematuria which was occasionally macroscopic.

HBsAg was detected in five of the patients, constituting the first group shown in the table. All of them received levamisole at a dose of 2.5 mg/kg/day for their antigenaemia but no beneficial effect of this drug has been observed. Two of these HBsAg carriers were randomly chosen not to receive any therapy and spontaneous remission was observed 2.5 to 10 years after the onset of their disease. Chronic liver disease was diagnosed by liver biopsy in one of these patients. The other three patients in the HBsAg group received corticosteroids; complete remission was achieved in two, at four weeks and eight years after the onset of the symptoms, respectively. The latter patient initially had a partial response to steroid treatment, then complete remission was noted three years after the cessation of treatment. Partial remission with persistent moderate proteinuria was noted in the last patient of HBsAg associated MGN group (patient number 4).

Idiopathic MGN patients constituted the second group. All of these five patients received steroid and subsequent steroid plus cyclophosphamide treatment. Complete remission was obtained in three (table). One of these children was in partial remission after a course of steroid and cyclophosphamide; he was then put on cyclic treatment with a three day course of bolus methylprednisone, alternating monthly with chlorambucil as described by Ponticelli *et al.*<sup>11</sup> Oral prednisone at a dose of 0.4 mg/kg/day was given in between. He is now in complete remission and off treatment after a year.

In the fourth patient of the idiopathic MGN group, the Ponticelli protocol was also instituted when no response was obtained with steroid

plus cyclophosphamide. Unfortunately there has been no improvement in the clinical or laboratory findings and the patient has recently been put on cyclosporin treatment. In the last patient a partial response has been achieved on the second month of steroid plus cyclophosphamide treatment.

Repeat biopsies were not performed in any of these patients.

### Discussion

The frequency of HBsAg in MGN was prominent in our study. HBsAg was present in 50% of our MGN cases whereas when our 632 patients with idiopathic nephrotic syndrome were screened only three had HBsAg markers (unpublished data). The prevalence of HBsAg in MGN is similar to the 45% reported from France.<sup>1</sup> On the other hand, in a childhood series from Japan all 11 patients had circulating HBsAg.<sup>5</sup> There have not been many reports relating the presence of the antigen to the prognosis of the glomerulopathy. Kleinknecht and Habib have stated that the prognosis in these patients was 'often favorable'.<sup>1</sup> Although our numbers are inadequate for statistical analysis it is obvious that there are no clear differences between the patients with HBsAg and those without. On the other hand, the patients associated with HBsAg had a rather younger age of onset of their disease. Idiopathic membranous glomerulopathy is known to be most common in the second decade of life.<sup>9</sup> As hepatitis B infection tends to occur somewhat earlier in developing countries, it may be suggested that HBsAg has induced the disease at an earlier age than expected by its natural course.

We have also attempted to analyse whether any of the clinical or laboratory features were relevant factors in prognosis and whether any of these helped to distinguish between the HBsAg related and idiopathic forms of MGN. In the 14 paediatric MGN patients reported from Canada,

hypertension was observed in 50% and was the only clinical finding that correlated with adverse outcome.<sup>7</sup> In our series 50% of the patients had occasional hypertensive values but it is hard to draw a similar judgment from our study group. Hypertension was not a feature that distinguished between the HBsAg and the idiopathic groups, being present in two and three children respectively.

When the nephrotic syndrome was present on initial presentation, the presence of haematuria and increased blood urea nitrogen did not appear to influence the final outcome adversely. Haematuria was present in 50% of the cases which was somewhat lower than the 80% and 57% percentages reported by others.<sup>1,7</sup> Haematuria was not a distinguishing feature between the groups.

Thus our results indicate that it is not possible to predict the prognosis of MGN from its clinical features as had been previously suggested in the literature. In our series there was no clinical finding that distinguished clearly between the idiopathic and HBsAg related forms of MGN. Our conclusion is consistent with the observations of Kleinknecht and Habib.<sup>1</sup>

Various reports in childhood series of MGN have concluded that steroids and immunosuppressive treatment do not have any clear achievements.<sup>2,7</sup> This is an important issue in the HBsAg related disease because it has been suggested that steroids might induce the replication of hepatitis virus and may accentuate the adverse effects of HBsAg carriers.<sup>12</sup> The fact that two of our patients entered remission without any treatment questions the beneficial effect of steroids in HBsAg related MGN. Thus immunosuppressive treatment should be used with caution in these cases. On the other hand, immunosuppressive treatment has had no adverse effect on the disease and led to a favourable course in most cases.

Ponticelli *et al*<sup>11</sup> have reported encouraging results in resistant MGN cases with a regimen of six months of pulse methylprednisone alternat-

ing with chlorambucil. A beneficial response was achieved in only one of our two patients put on this regimen. This protocol should be tested on more cases of idiopathic MGN before any judgments are drawn.

Overall complete remission was achieved in four of five HBsAg related MGN cases and in three of the five idiopathic cases. There was a partial remission in one patient in each group, but these were followed up for only one year. Although we cannot predict the outcome of these two patients, it can be stated that our MGN cases had a favourable course and we suggest that immunosuppressive treatment should be tried, especially in the idiopathic form of MGN.

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