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Membranous nephropathy in childhood and its treatment

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Abstract. Membranous nephropathy is predominantly a disease of middle-aged and elderly individuals, and is thus rather an uncommon finding in proteinuric and nephrotic children. In children, it differs in several important respects from the disease as seen in adults: an apparent associated cause is more common, macroscopic haematuria is seen quite frequently, a relapsing course is more often noted, renal venous thrombosis is not found and evolution into renal failure is the exception. Nevertheless, a proportion of children with membranous nephropathy *do* evolve into renal failure, and their management is discussed with particular reference to recent papers on the treatment of membranous nephropathy in adults. An aggressive search for associated disease is worthwhile in children, and one should wait to see what the evolution or proteinuria and renal function may be. If a progressive course becomes evident, then a trial of treatment with corticosteroids is worthwhile, but if this is ineffective then a more aggressive approach involving the use of alkylating agents may be justified. It remains undetermined what the best regime in children and adolescents may be.

Key words: Membranous nephropathy – Proteinuria – Nephrotic syndrome – Prednisone – Prednisolone – Hepatitis B – Chlorambucil

Introduction

Recently, there has been considerable discussion on the treatment of membranous nephropathy in adults. This discussion has been confused and confusing; what conclusions may the paediatric nephrologist, who rather rarely sees membranous nephropathy, draw from this and the literature available describing childhood cases?

The histological appearance now called membranous nephropathy was first recognized 60 years ago on optical microscopy through the use of new staining techniques. Its histomorphology, on both electron and immunofluorescent microscopy, is now well recognized and has been excellently described in detail elsewhere [1]. From work on animal models, it seems that this appearance is not so much the result of a single aetiology, but occurs through the intervention of a particular immunopathological process [2–4]: the formation of auto-antibodies directed against cell-surface antigens present in the glycocalyx of the epithelial cells (podocytes) of the glomerulus. By a process of capping and shedding, these antibodies, together with the relevant cell-surface antigen, a glycoprotein present in the clathrin-coated pits on the cell surface, come to lie as immune aggregates in the outer part of the capillary basement membrane (lamina rara externa) beneath the foot processes of the podocytes, whose structure is variously altered.

Although there is no direct evidence as yet that such a process operates in human membranous nephropathy, and the antigen(s) of the human disease remain unidentified, it seems very likely that some similar mechanism is involved [3]. An alternative mechanism is that cationic antigens unrelated to the glomerulus may become "planted" in the lamina rara externa, their passage to this site being facilitated by electrostatic interaction with the fixed glomerular polyanion present on the capillary basement membrane [5]. Subsequently, antibody (again possibly with a cationic charge) fixes to these "planted" antigens. Perhaps these two mechanisms both operate in one case or another, or even together. It now seems very unlikely that circulating preformed immune complexes, either soluble or insoluble, play any role in the genesis of subendothelial deposits as seen in membranous nephropathy.

The proteinuria so characteristic of membranous nephropathy arises in animal models from deposition of complement along the capillary walls, and in particular the C5b–9 membrane attack complex [2, 3, 6]. In the human disease, C5b–9 is present in a similar site. Proteinuria is independent of cell recruitment, proliferation or infiltration, which is in line with the relatively acellular appearance of the glomeruli in the human disease. The C5b–9 complex is also capable, in vitro, of stimulating synthesis

Table 1. Extra-renal conditions associated with membranous nephropathy in 100 children (data of Kleinknecht and Habib [19], rearranged)

Condition	No. of patients
Hepatitis B	18
Arthralgias and/or skin rash	5
Systemic lupus erythematosus	4
Streptococcal infection	4
Idiopathic thrombocytopenia	3
Proximal tubular dysfunction	3
Sickle cell disease (SS or AS)	3
D-Penicillamine	1
Syphilis	1
Leukaemia (myelomonocytic)	1
Total	43/100

Table 2. Membranous nephropathy: associated conditions in adults (data of Cahen et al. 1989 [20] and Adu and Cameron 1989 [21]

	Cahen (82 patients)	Adu and Cameron (253 patients)
Hepatitis B	1	1
Drug-associated	5[a]	18[b]
Neoplasia	4	9
Secondary syphilis	1	1
Systemic lupus erythematosus	4	19[c]
Thyroiditis	3	4
Rheumatoid arthritis	–	2[d]
Paraproteinaemia	–	1
Diabetes mellitus	1	5
Total	19/82 (23%)	60/253 (24%)

[a] D-Penicillamine 3, captopril 1, fenoprofen 1
[b] D-Penicillamine 12, gold 6
[c] Four clinical lupus; 15 ANF positive
[d] Not treated with penicillamine or gold

of type IV collagen by isolated glomeruli [7] and thus the characteristic glomerulosclerosis may also be explained as the result of complement activation.

Thus we should expect to see a pattern of membranous nephropathy whenever these mechanisms of pathogenesis and injury are evoked, and one could predict that, first, there would be a number of associated diseases or clinical circumstances in which membranous nephropathy might be found, and second, that the evolution would be very variable. Both of these predictions turn out to be correct.

Membranous nephropathy in childhood

Prevalence

It is almost impossible to estimate how frequently, or infrequently, membranous nephropathy might be found in children with isolated symptomless proteinuria, because of differing policies with regard to renal biopsy in different units and in different countries. Even when a nephrotic syndrome is present, it is no longer usual in most units to biopsy *all* nephrotic children, so only historic data are available to us. Data from the International Study of Kidney Disease in Children (ISKDC) [8], in which *all* nephrotic children were biopsied in 21 centres from 11 different countries, showed that only 4 of 400 consecutive children under 15 years with an *idiopathic* nephrotic syndrome had a membranous nephropathy (0.8%). However, the *total* incidence will vary greatly from country to country, along with the incidence of associated disorders. In Japan, 6.7% of biopsied children were reported as having membranous glomerulopathy [9], the majority with hepatitis B, and a similar pattern is seen in North [10], Central [11] and Southern Africa [12], other parts of the Far East [13] and some areas of Europe, such as Poland [14], Southern Italy [15] and Spain [16]. In some parts of the world syphilis-associated membranous nephropathy accounts for a significant proportion of cases [17, 18]. Equally, given the declining incidence of minimal change disease with increasing age during childhood, an older nephrotic child is rather more likely to have membranous nephropathy than those aged 1–5 years, although the condition has been observed even during the 1st year of life [19]. Our own youngest patient was 8 months of age, but the morphology of the renal biopsy was atypical. Some cases of congenital syphilis may present, of course, as neonatal nephrotic syndromes [17, 18].

Membranous nephropathy with associated diseases

The largest series [19] showed that 43 of 100 (43%) children with membranous nephropathy had some associated disorder (Table 1). However, in our own series of 30 children and adolescents (S. M. Chapman, C. Chantler, J. S. Cameron, unpublished work) the proportion was lower. Only 8 children (23%) had associated features, 4 being hepatitis B positive, 1 with a streptococcal infection, and 1 with a Wilms' tumour. A further patient had anti-smooth muscle antibody and another unexplained splenomegaly. In recent studies in adults, comparable figures were 19 of 82 (23%) from Cahen et al. [20] and 60 of 253 (24%) from the British glomerulonephritis registry [21] (Table 2). Thus children more frequently show an associated disorder than adults, and associated disorders, especially infections such as hepatitis B and syphilis, are worth screening for. In contrast to adults, associated malignancies are rare in children. An anti-nuclear factor and DNA binding should be done in all children with membranous nephropathy, because systemic lupus erythematosus (SLE) may be already present, or develop later. Another association (not represented in Table 1) is that with deficiencies of complement components, especially C2. These patients may present with membranous nephropathy [22] and later develop SLE [23]. Other infections have been more rarely reported in association with a membranous pattern of glomerulopathy: streptococci, as in our own series and that of Kleinknecht and Habib [19], echinococcus, *Plasmodium malariae* or filariasis.

One curious feature is that, despite the very well-recognized association, on the one hand, between infants with a

Table 3. Outcome in membranous nephropathy in childhood (data of Kleinknecht and Habib [19] and S. M. Chapman, C. Chantler, J. S. Cameron, unpublished)

Status at last investigation	All patients		Patients followed >3 years
	Kleinknecht/Habib	Chapman	Kleinknecht/Habib
Complete remission	44	10	38
Isolated microscopic haematuria	1	–	–
Proteinuria <0.5 g/24 h	13	1	7
Proteinuria >0.5 g/24 h	20	8	13
Nephrotic syndrome	9	3	4
Renal failure	9	3	9
Dead	–	1	–
Total	96	26[a]	71

[a] Four patients lost to follow-up; all but 2 patients followed >3 years

Table 4. Treatment given in the four controlled trials

Group	Drug(s) used	Dosage	Duration of treatment	Year of report	Author	
American Interhospitals' study	Prednisone	125 mg alternate days	8 weeks	1979	Coggins	[40]
Toronto glomerulonephritis study group	Prednisone	45 mg/m^2 alternate days	6 months	1989	Cattran	[42]
Medical Research Council of UK trial	Prednisone	125 mg alternate days	8 weeks	1989	Cameron	[43]
North Italian trial	Methylprednisolone alternating monthly with	0.4 mg/kg per 24 h	4 weeks	1984/1989	Ponticelli	[41]
	Chlorambucil	0.2 mg/kg per 24 h	4 weeks			
	and monthyl injections of 3 g methylprednisolone i. v. × 6					
	Total duration of treatment		6 months			

congenital nephrotic syndrome and acute renal venous thrombosis [24] and, on the other, between adults with renal venous thrombosis and membranous nephropathy [25], renal venous thrombosis appears to be unrecorded in the childhood membranous disease. The youngest patient I have been able to find with chronic renal vein thrombosis was aged 14 at onset and mentioned without details of histology in the report of Llach et al. [25]. One of the original reports, that of Derow et al. in 1939 [26], describes a 15-year-old with a nephrotic syndrome, renal venous thrombosis and diffusely thickened capillary walls in the glomeruli, but none of the reports of childhood membranous nephropathy reviewed [27–32] mention any case. We have never seen such a case, although one 14-year-old boy with SLE and membranous nephropathy thrombosed his vena cava.

Clinical presentation

In Kleinknecht and Habib's series [19], 70 of 96 cases (excluding those 4 with SLE) had a nephrotic syndrome at onset. The remainder had symptomless proteinuria and 6 also had macroscopic haematuria. Altogether gross haematuria was seen at some time in 19 of 96, whilst in adults it is exceptionally rare. Microscopic haematuria was present in 80% of cases. In the collected data from the literature [19, 27–32], males outnumber females, although in our own series the female to male ratio was, in contrast 1.9:1. Hypertension was present in only 4% of the series of Kleinknecht and Habib, but in as many as 11 of 30 in our own series. Kleinknecht and Habib [19] report in detail an interesting subgroup of children with severe and disproportionate proximal renal tubular dysfunction, but we have not seen this yet. Apart from those rare cases with inherited complement deficiency of C2 [22, 23], a low C3 and C4 may be seen on occasion in children but almost never in adults.

Clinical course

In contrast to adults, in whom one-fifth to one-half of patients with untreated idiopathic membranous nephropathy and a nephrotic syndrome go into renal failure within 10 years [33–37], this course is unusual in children. In Kleinknecht and Habib's series [19], only 9 of 71 children followed for 3 years or more showed renal failure, with another 4 still having a full nephrotic syndrome (Table 3). In our own series, only 3 adolescents aged 14, 15 and 19 years at onset have gone into renal failure and required transplantation. In Kleinknecht and Habib's series, of 70 patients with a full nephrotic syndrome at onset, this remitted in the majority between 12 and 18 months from onset. Some of this relatively benign outlook arises from the high proportion of patients with secondary nephrotic syndrome, which even in adults (unless the underlying disease is a malignancy) do well also. Thus in children,

Table 5. Results of recent controlled trials in idiopathic membranous nephropathy in adults; post-treatment status of nephrotic patients

Trial	Follow-up (months)	In trial *n*	Remission *n*	Proteinuria *n*	Renal Failure[a] (of whom dialysis/Tx) *n*	Significance
Interhospitals' USA	26–52	C 38	5[c]	22	11	
		Rx 34	7[d]	25	2	$P<0.05$
Canadian[b]	48± 3	C 54[b]	20	28	6 (4)	
		Rx 54[b]	23[f]	24	7 (3)	$P>0.05$
MRC UK	52± 6	C 51	7	29	15 (8)	
		Rx 52	12[i]	31	11 (6)	$P>0.05$
Italian	60 (median)	C 39	7[h]	28[e]	4 (4)	
		Rx 42	23[g]	18	1 (1)	$P<0.05$

Note: Patients who died of incidental causes or were lost to follow-up are considered as at their last observed renal status

[a] Renal failure is taken to mean a plasma creatinine in excess of 4 mg/dl or 400 μmol/l. In the Italian trial, in the control group at last follow-up 3 patients had plasma creatinines of 397, 397 and 371 μmol/l

[b] In the Canadian trial only data on the 108 patients who had proteinuria in excess of 3.5 g/24 h are considered here

[c] One patient subsequently relapsed

[d] Four patients subsequently relapsed

[e] Four patients subsequently relapsed

[f] Eight patients subsequently relapsed

[g] Seven patients subsequently relapsed

[h] Five patients subsequently relapsed

[i] Four patients subsequently relapsed

after searching for an underlying cause and treating it if possible, it is always worth waiting for at least 1 year to see what the evolution of the nephrotic syndrome (if present), or the proteinuria, may be. There is no evidence that treatment of patients with hepatitis B and membranous nephropathy with steroids improves their outlook, which is in any case good; only one of the patients of Kleinknecht et al. [32] went into renal failure.

Treatment

Certainly there is even less justification in children than in adults for treating *all* patients with idiopathic membranous nephropathy. There is no doubt that the prognosis of adults with less than nephrotic range proteinuria is usually good, and much better than those with a full nephrotic syndrome [38], and the same seems to be true in children. Therefore one should simply observe these patients with symptomless proteinuria, the majority of whom will get better – although a nephrotic syndrome may occur subsequently, as in ten children reported by Kleinknecht and Habib [19].

Nevertheless, we are still faced with the problem of what we should do about the minority of children with membranous nephropathy and persistent proteinuria, a nephrotic syndrome and declining renal function evident after perhaps 1–2 years of follow-up. No series of children has included a sufficient number of such cases to draw any firm conclusions, and in adult nephrology controversy rages. Because of the very variable outcome of the condition, it is very important that any comparisons be made between carefully matched patients. The extensive and conflicting retrospective uncontrolled data in adults (reviewed recently [39]) give less information than usual because of this important point. Age, sex, degree of proteinuria, MHC antigens, hypertension, staging of glomerular and interstitial changes and, of course, associated diseases have all been alleged to affect outcome [33, 36, 37], and in none of the retrospective reports were these points fully controlled, if at all.

Therefore, here we will consider in detail only the results of four recent carefully controlled prospective trials [40–43] (Table 4), performed within the last decade, together with some additionall new anecdotal data on the later treatment of adults who already had considerable loss of function. We will also ignore several previous trials in which the number of patients was too small to justify the negative conclusions drawn (see [39]).

These four recent trials (Table 4) examined the question of whether treatment with immunosuppressive agents, prednisolone alone or with an alkylating agent, would affect the medium-term outcome of adults with idiopathic membranous nephropathy. The retrospective rationale for using such agents has been discussed above. In all four trials, known causes of membranous nephropathy were carefully excluded, and in three of the trials only patients with a full nephrotic syndrome were included. In the Canadian trial [42], patients with subnephrotic proteinuria were randomized also, but nephrotic patients were analysed as a subgroup.

The treatments given are summarized in Table 4. All trials included prednisone, prednisolone or methylprednisolone; only the Italian trial added an alkylating agent, chlorambucil. Treatment was more prolonged in the Italian [41] and Canadian [42] trials, but the dose was higher in the UK [43] and American [40] trials, which were essentially the same. Clearly the Italian trial employed much more intense immunosuppression than any of the other trials.

All trials entered enough patients for a clinically significant effect to emerge if one were present. The American

trial and the Italian trial were judged by those reporting the results to have shown a beneficial effect of the treatment on the evolution of the disease; the Canadian and British trials concluded that no effect had been observed (Table 5). Further analyses of rates of decline in renal function or rise in plasma creatinine, or mean protein excretions, confirmed the general conclusions shown in Table 5. Factors predictive of a poor outcome were the presence of tubulointerstitial lesions in the renal biopsy, a raised plasma creatinine at randomization, female sex, and the degree of proteinuria, together (in the American and Italian trials) with the absence of treatment. Hypertension and glomerular histology, rather surprisingly, were not predictive factors.

The different behaviour of the control groups is worth noting: in the American and UK trials, a considerable proportion of patients went into renal failure in the control group, whereas in the Italian trial, even amongst those who received no treatment, very few of the controls evolved into uraemia within 6 years (Table 4).

In the light of these conflicting results, what should the individual paediatrician treating a particular patient now do? A major problem in using the Italian regime, which has given the best results reported so far, is the use of a dose of chlorambucil in a non-malignant condition for a total of 3 months at a dose of 0.2 mg/kg per 24 h – about 20 mg/kg in total. In other workers' hands, both the tolerance of this dose of chlorambucil has been lower in terms of leucopenia and gastrointestinal upsets [44–47], and the effectiveness on renal functional decline has been much poorer or absent [45–47]. The oncogenic effects and gonadal toxicity of this regime have not been evaluated in adults, far less in children, although data are available on the effects of 3 months' treatment with chlorambucil at lower dosages in children with minimal change nephrotic syndrome [48]. Thus, this regime should only be used, if at all, in patients in whom clear deterioration in renal function is evident. Support for this course of action comes from the studies of Mathieson et al. [44] and West et al. [49], who used cyclophosphamide instead of chlorambucil. These studies showed this regime to be effective in adults with already declining renal function, but the studies were small and not controlled. (The study of West et al. [49], despite its title, was a retrospective case-comparison study and not a prospective controlled trial.)

But what of steroids? Should they, as a sole treatment, be abandoned? The American study [40] suggest not, although this study (like all of those in Tables 4 and 5 can be criticized. Also, Hopper [50] has pointed out again recently that maybe the problem lies in the duration and intensity of the steroid treatment. The Italian trial [41] and analysis of published data on the use of cytotoxic agents [51] both suggest that more intense immunosuppression may be effective when less intensive suppression is not; could this more intense suppression be achieved with steroids alone, and would this be the best strategy in terms of benefits and unwanted side-effects?

Many paediatricians will still prefer, having identified the older child or adolescent who has progressive disease, to try first the effect of prednisolone alone. Two recent studies from the UK [52, 53] on the late treatment of patients with declining renal function using prednisolone or methylprednisolone alone, and similar unpublished data from our own unit in ten patients, suggest that this attitude is justified. Results similar to those of Mathieson et al. [44] and West et al. [49] were obtained, but using prednisolone or methylprednisolone alone without the addition of an alkylating agent. In the British MRC trial [43], nine patients were withdrawn from the trial and given "late" treatment in this fashion by the participating physicians. Dosages varied, but in three patients a dramatic improvement in plasma creatinine was observed, a fourth patient was able to stop long-term dialysis, and in the remainder the fall-off in renal function was temporarily halted but the decline in renal function reasserted itself. Hopper's [50] recommendation is a dose of 200 mg on alternate days in adults, higher than in any of the trials described in Tables 4 and 5; the equivalent dose for children would be about 120 mg/m^2 per 24 h.

A final pointer to the fact that at least a subgroup of patients with membranous nephropathy are responsive to steroids alone, or more intense immunosuppression, comes from the observation of occasional children who run a typical steroid-sensitive relapsing course, but show classical membranous nephropathy on renal biopsy (T. M. Barratt, unpublished observations). Rather more common are patients with occasional relapses, as noted above, who appear to respond repeatedly to treatment [19, 54].

Thus many aspects of the treatment of children with membranous nephropathy, indeed the majority of aspects, remain unclear. However, the principles of first identifying secondary forms, then waiting to see what the evolution may be, remain applicable. I would still prefer next to try steroids on an alternate-day basis, in as high a dose as seems tolerable to patient and doctor for 6 months, despite the negative results of the Canadian and UK trials in adults. To date, we have never treated a child with the Italian regime including chlorambucil, and only a collaborative study could generate enough patients for a proper trial to be organized.

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