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Treatment of mesangiocapillary glomerulonephritis

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Mesangiocapillary glomerulonephritis (MCGN), also called membranoproliferative glomerulonephritis, is a relatively uncommon histopathologic entity characterized by mesangial expansion, endocapillary cellular increase, and capillary wall thickening[1-4]. Two main types can be distinguished histologically, type I with subendothelial deposits and type II with electron-dense deposits in the lamina densa of the glomerular capillary basement membranes. Type III MCGN is probably a variant of type I with subepithelial «humps» in addition to the subendothelial deposits. MCGN was intially characterized by its association with persistent hypocomplementemia, but as many as one-half of patients with type II MCGN can have persistently normal serum levels of the C3 complement components. An IgG autoantibody that prevents the decay of C3 convertase by a C3b inactivator (C3 nephritic factor) is found in the majority of patients with type II MCGN but only at low concentrations in a small fraction of patients with type I MCGN. Type I MCGN is frequently idiopathic (primary MCGN), but it can also be found in association with a variety of diseases with chronic antigenemia such as infections, systemic or malignant diseases, and complement deficiency states. Type II MCGN is more rare than type I; its causa is not known and it can be associated with partial lipodystrophy[1-4].

Treatment of Primary Mesangiocapillary Glomerulonephritis

The treatment of primary MCGN has been and continues to be a controversial subject[1-5]. There have been no long-term studies comparing the survival and morbidity of patients with MCGN on a given therapy with those of concurrent, randomly assigned control patients similarly followed and matched for control of hypertension, hyperlipidemia, and protein intake. The information available is based on uncontrolled or retrospective studies using historical controls and short-term, randomized controlled trials. Before discussing the results of these investigations, it seems appropiate to review the factors that render difficult their interpretation and invalidate the use of historical controls:

a) *Variability of MCGN.* Usually MCGN is a progressive disease, but spontaneous improvements and even remissions can occur. Features associated with the worst prognosis are persistent nephrotic syndrome or macroscopic hematuria, hypertension, a deteriorating renal function at presentation, and the presence of crescents or glomerulosclerosis on the renal biopsy[1,2]. Adult and type II MCGN patients have a worse prognosis than children and type I MCGN patients. The effect of pregnancy on the natural history of MCGN is impredictable. Although the majority of patients have an uncomplicated course if hypertension is absent and renal function is normal[4,6,7], pregnancy may accelerate the deterioration of renal function in some patients[8-10]. In addition to the variability of the disease in different patients, the pattern of the disease in developed countries may be changing[11-13]. This is suggested by the studies in France, Italy, and Spain indicating that the incidence of MCGN is declining, possibly as a result of changes in the incidence of bacterial and viral infections, better preventive medicine, and modifications in immune responsiveness.

b) *Nonspecific mechanisms of progressive glomerular injury.* It has become evident in vecent years that systemic and glomerular hypertension, hypertension, hyperlipidemia, and dietary protein may play a major role in the progression of glomerular injury in patients with a variety of glomerular diseases[14-16]. One of the problems with the use of historical controls is that major changes have occurred over the years in the awareness and interventions to control these risk factors. Hypertension may be especially important in MCGN since glomerulosclerosis of «hyperpefusion injury» is seen in this disease with a higher frequency than in other forms of glomerulonephritis[17]. Experimentally, it has been demostrated that antihypertensive therapy can reduce the hypertension induced glomerular injury and that converting enzyme inhibitors are more effective than triple therapy with hydralzine, reserpine, and hydorchlorothiazide[18]. Converting enzyme inhibitors have been shown to significantly reduce the proteinuria in patients with glomerular diseases including MCGN[19]. Thus, both the adequacy of blood pressure control and the type of antihypertensive medications are im-

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portant and need to be carefully controlled in therapeutic trials. Hypercholesterolemia is the major lipid abnormality in the nephrotic syndrome[20]. Experimentally, the control of the hypercholesterolemia results in a reduction of glomerular damage[15]. Whether hypercholesterolemia contributes to progressive glomerular injury in glomerular diseases associated with the nephrotic syndrome is uncertain. The treatment of hyperlipidemia in the nephrotic syndrome has been the subject of excellent reviews[20] and includes dietary modifications (low cholesterol and saturated fatty acids and antilipemic agents (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors alone or in combination with bile acid sequestrants or probucol, or the combinatios of nicotinic acid and bile acid sequestrants). Finally, the dietary protein prescription has changed markedly in the last few yers. Until recently, patients with the nephrotic syndrome were prescribed high protein diets to compensate for the urinary protein losses. This practice has now changed because of the experimental data indicating that excessive dietary protein can contribute to glomerular hyperfiltration and glomerulosclerosis[16]. Clinical trials have suggested that the beneficial effect of protein-restricted diets on the progression of renal insufficiency is observed mainly in the patients with primary glomerular diseases[21, 22]. Furthermore, recent studies have shown that a reduction of the protein intake in patients with the nephrotic syndrome for from 1.6 to 0.8 g/kg/day reduces the albumin catabolic rate to lower than normal levels, while the albumin synthetic rate, although reduced, remains within the normal range, the proteinuria decreases and the serum albumin concentration increases[23].

c) *Statisfical flaws.* Many retrospective studies have constructed survical curses plotted after the clinical onset of the disease and compared these curves with those of historical controls from studies on the natural history of MCGN[24-26]. In a recent reassessment of treatment results in MCGN, Donadio and Offord have pointed out a major problem with these comparisons[27]. The treatment for the patients in these retrospective studies usually started many years after the clinical onset of the disease. Thus, the patients in the treatment groups were given 100 % survical between the clinical onset and the initiation of therapy, while this was not the case in the historical controls.

Short-Term Uncontrolled or Retrospective Studies

Several short-term uncontrolled or retrospective studies using glucocorticoids, cytotoxic agents, anticoagulants, antiplatelet agents, and nonsteroidal anti-inflammatory drugs (NSAID), either alone or in combination, are summarized in Table I[28, 32]. The number of patients are small. The patients in three of these studies[28, 31, 32] had a particularly severe disease with advanced renal insufficiency, nephrotic-range proteinuria, and often crescents in the renal biopsy. Although a few of them had dramatic apparent responses to therapy, remissions of an acute deterioration of renal function with acute nephritis superimposed on MCGN have also been observed in untreated patients[33]. An improvement in renal function occured in 17 of 29 patients, but the periods of follow-up were short. A later report on one of the series indicated that eventually most of the patients required dialysis[2]. Therefore, the questionable benefits of aggressive immunosuppressive and/or anticoagulant therapy in these patients must be carefully weighed against the potential riks. In addition to the treatments outlined in Table II, plasmapheresis has been used in 17 patients with MCGN and deteriorating renal function[34-37]. In 3 patients, there was no follow-up. Seven patients had no discernible benefit. Six patients might have benefited from plasmapheresis, but their long-term outcome has not been reported. One patient with type I MCGN was maintained on plasmapheresis from three times weekly to once every three weeks for more than three years with stabilization of renal function[37].

Long-Term Uncontrolled or Retrospective Studies

Several long-term uncontrolled or retrospective studies are summarized in Table II[21, 38-41]. The number of patients were larger and they had milder disease than those in the short-term studies reviewed above. Treatments included prednisone alone or in combination with other immunosuppressive agents and/or anticoagulants, NSAID, and antiplatelet agents. The 10-year cumulative survival free of renal failure ranged between 60 and 90 %, as compared to 40-50 % in historical controls[24-26]. Unfortunately, these comparisons are flawed because prognositically important factors were not necessarily similar, changes have occurred in the general management of these patients, and, most importantly, major bias in favor of the treatment groups was introduced by contructing the survival curves from the time of onset of the disease, which is years before any therapy was started[27].

Randomized Controlled Studies

Seven prospective, randomized controlled studies are summarized in Table III[33, 42-48]. The duration of therapy in these estudies ranged from 2 to 41 months. As in the case of the long-term retrospective studies, the patients usually had less severe disease than those in the short-term restrospective studies. Azathioprine or chlorambucil were found to have no favorable effect on renal function or proteinuria[42]. Two clinical trials used triple-drug therapy with cyclophosphamide, dipyridamole, and warfarin, which had been previously shown to benefit patients with MCGN in an uncontrolled study. No significant effect on renal function or proteinuria were detected[33, 43]. The preliminary results of the International Study

Table I. Short-term uncontrolled or retrospective studies

Author, yr (reference)	N.° pts.	Age ¶ (yrs)	Risk profile * (N.° pts.)	Treatment *	Duration of treatment	Improved + renal function (N.° pts.)	Proteinuria <0.5-1 g/ 24 hr (N.° pts.)	Improved histology (N.° pts.)	Complications
Kincaid-Smith, 1972[28]	16	30	Scr≥2 (14) N. syn. (16) HT (15) Crescents (4) MCGN II (5)	Cy 1.5-2.5 mg/kg/d+ DIP 100 mg quid+AC to PT 2.5x	4-55 mo	(10)	(5)	(4)	Death from respiratory failure (1)
Michielsen, 1973[29]	16	9-54	C_{cr}<60 (5) N. syn. (8)	IND 75-150 mg/d+AZ (4) or CY (2)	6-73 mo	(1)	(4)	(0)	Perforated duodenal ulcer (1)
Vanrenterghem, 1975[30]	9	NA	C_{cr}<60 (5) N. syn. (5)	IND 75-150 mg/d+CY 50 mg/d	18-36 mo	(4)	(6)	NA	None
Cole, 1976[31]	3	6-13	C_{in}<30 (3) N. syn. (3) MPGN II (2)	MP bolus 30 mg/kg qodx6 +P (3) or AZ (1)	3-12 mo	(2)	(0)	NA	None
Chapman, 1980[32]	10	6-13	C_{EDTA}<60 (10) N. syn. (8) Crescents (7) MPGN II (4)	P 0.25-2 mg/kg qod+ AZ 2 mg/kg/d +DIP 10 mg/kg/d +AC to PT 2x	6-69 mo	(5)	NA	(3)	Cellulitis (1) H. zoster (1)

¶ = mean or range. NA = not available.
* Scr = serum creatinine (mg/dl); C_{cr}, C_{in}, C_{EDTA}, C_{ioth} = clearance of endogenous creatinine, inulin, EDTA, iothalamate (ml/min/1.73 m^2); N. syn. = nephrotic syndrome, HT = hypertension.
* P = prednisone, MP = methylprednisolone, AZ = azathioprine, CY = cyclophosphamide, IND = indomethacin, DIP = dipyridamole, AX = anticoagulants (phenindione, warfarin of Coumadin), ASA = aspirin, CHL = chlorambucil, ME = mechlomethamine, PT = prothrombin time.
+ = improvement = >25 % increase in clearance or >25 % reduction in serum creatinine.

Table II. Long-term uncontrolled or retrospective studies

Author, yr (reference)	N.° pts.	Age (yrs)	Risk profile (N.° pts.)	Treatment (N.° pts.)	10-year renal survival *	Complications (N.° pts.)
McEnery, 1986[38]	45	2-17	Scr > 1.5 (8) N. syn. (15) HT (19) Crescents (7)	P 2-2.5 mg/kg qod → 0.3-0.8 mg/kg qod over 4 yrs+ ME (11) or CY (1) or AZ (1) or ASA/DIP (6)	74 %	Growth deceleration; cataracts (8)
Narita, 1987[39]	107	NA	NA	P+CY (57) or P+ CY+DIP+AC (29) or NSAID+DIP (19)	60-80 %	NA
Lagrue, 1988[40]	53	17-77	Scr>1.7 (1) N. syn. (41) HT (5) MPGN II (2)	NSAID	85 %	Hyperkalemia (3)
Orlowski, 1988[41]	40	25	«Incipiente renal failure» (15) N. syn. (40) HT (28)	P 2 mg/kg qod+ AZ 1.5 mg/kg/d +CY 0.5-1 mg/kg/d or CHL 2 mg qd	91 %	Diabetes mellitus (3), peptic ulcer (3), cataracts (9), pulmonary tuberculosis (1)
Donadio, 1989[27]	32	6-72	C_{ioth}<65 (10) PrU 5.9	DIP 75 mg tid+ ASA 325 mg tid	70 %	Gastric ulcer (1), rectal bleeding (1), painful ecchymosis

Abbreviations = see Table I.
* From onset of disease.

Table III. Randomized prospective trials

Author, yr (reference)	N.° pts. (treatment/ control)	Age	Risk profile	Treatment (N.° pts.)	Duration of treatment	Renal function	Protei-nuria	Complications
Lagrue, 1975[42]	34/9	NA	Scr<1.5 PrU>1	AZ 2-3 mg/kg/d (18) or CHL 0.1-0.2 mg/kg/d (16)	12 mo	NS	NS	9 pts. (5 AZ, 4 CHL) discontinued treatment because of complications
Tiller, 1981 [43]	37	NA	NA	CY+DIP+AC	36 mo	NS	NS	NA
ISKDC*, 1982[44]	23/14	5-16	C_{cr}>40 PrU>40 mg/hf/m^2	P 40 mg/m^2 qod	NA	Protective (P<0,1)	NA	Toxicity negated potencial benefit
ISKDC**, 1987[45]	47/33	5-16	C_{cr}>40 PrU>40 mg/hr/m^2	P 40 mg/m^2 qod	41 mo	Protective (P<0.1)	NA	NA
Zimmerman, 1983[46]	10/8	21	Scr 1.6 PrU 6.2	DIP 100 mg qid +AC to PT 2x	12 mo	Stabilized	NS	Cerebral hemorrhage (1), menorrhagia (2), epistaxis (2), bleeding ulcer (1), abdominal wall hematoma (1)
Donadio, 1984[47]	21/19	6-72	C_{Ioth} 69 PrU 5.9	DIP 75 mg tid+ ASA 325 mg tid	12 mo	Stabilized	NS	Gastric ulcer (1) rectal bleeding (1), painful ecchymosis (1)
Cattran, 1985[33]	32/27	6-77	C_{Cr} 69 PrU 5.0	CY 1.5-2.0 mg/kg/d +DIP 100 mg quid +AC to PT 2-2.5x	18 mo	NS	NS	Infection (2), hematuria (2), hemoptysis (2), alopecia (1)
Laurent, 1987[48]	14/12 *	15-62	Scr<1.7 PrU 0.7-7.4	Diclofenac 100 mg/d	2 mo	NS	70 % reduction	Intolerance (1)

Abbreviations = see Table I.
* International Study of Kidney Disease in Children. The control group in this study had a longer duration of disease than the treatment group.
* This study includes 12 patients with IgA glomerulopathy.

of Kidney Disease in Children have been published in 1982 and 1987 in abstract form only[44, 45]. These studies showed a protective effect on renal function of borderline statiscal significance, but this possible gain was negated by the occurrence of significant toxicity. Another trial with warfarin and dipyridamole resulted in stabilization of renal function without significant effect on proteinuria but had major hemorrhagic complications[46]. Antiplatelet drugs alone also resulted in a short-term stabilization of renal function and were better tolerated[47], but the long-term follow-up of these patients, after the code was broken and some patients in the placebo group were started on treatment, has not clearly demonstrated a long-term beneficial effect[27]. Finally, a two-month trial of a nonsteroidal anti-inflammatory drug, diclofenac, demonstrated significant reduction in proteinuria without an effect on renal funcion[48]. In summary, the results of these randomized controlled studies do not allow any specific recommendation for a proven successful therapy of MCGN. Although antiplatelet drugs have few side effects and may have a beneficial effect, they certainly do not stop the progression of the disease. The remaining treatment modalities have considerable side effects which need to be carefully weighed against the questionable benefits.

Recurrent MCGN After Renal Transplantation

Recurrence of the disease occurs in approximately 20 to 30 % of patients with type I MCGN and approximately 90 % of the patients with type II MCGN[4, 49-51]. As much as 20 to 50 % of the patiens with recurrent disease lose their grafts, but the course to end-stage renal failure can be very slow. Because of the frequency of disease recurrence and the possibility of subsequent graft loss, some authors have discouraged the use of living related donor grafts in type II MCGN[4]. There are no good predictors for recurrence of type I MCGN with the possible exceptions of a rapidly progressive course with glomerular crescents in the native kidneys and the history of recurrent disease in a previous renal allograft[4]. The immunosuppressive

program for renal transplantation is obviously inadequate to prevent disease recurrence. Whether the frequency of recurrence has changed during the cyclosporin era is uncertain. Antiplatelet drugs are of limited protective value[52]. Plasmapheresis has been used successfully for a recurrent crescentic type II MGCN[53] and with mixed results in two patients with recurrent type I MCGN[34, 54].

Treatment of Secondary MCGN

The treatment of the secondary forms of MCGN depends on the nature of the associated diseases. Recombinant human alpha-interferon has been used in patients with chronic active hepatitis and glomerulonephritis[55-58]; several patients with membranous glomerulopathy had a remission of the nephrotic syndrome, but the only patient with MCGN did not have a serological or clinical response to interferon therapy[57]. On the other hand, a healthy carrier of hepatitis B surface antigen with associated MCGN had a remission of the nephrotic syndrome following the administration of intravenous methylprednisolone which coincided with a marked increase in the HBsAg titer; the authors hypothesized that the extreme antigen excess might have inhibited the glomerular deposition of immune complexes[59]. Glucocorticosteroids in combination with Dapsone and rifampin resulted in a marked improvement of renal function and a remission of the nephrotic syndrome in a patient with leprosy and associated MCGN[60]. On the other hand, the MCGN associated with the hepatosplenic form of schistosomiasis mansoni has not been influenced by antiparasitic or immunosuppressive therapy, may be due to the duration of the infection prior to the initiation of treatment[61]. Indomethacin has been successfully used in a patient with type I MCGN and sarcoidosis[62]. Cyclosporin resulted in a dramatic improvement in a patient with MCGN associated with Buckley's syndrome, which is characterized by recurrent infeccions, atopic eczema, increased serum IgE levels, and abnormal granulocyte chemotaxis[63]. Finally, the administration of fresh frozen plasma to patients with a congenital C3 deficiency and MCGN was without therapeutic benefit[64].

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