Survival Analysis of Thai Patients with IgM Nephropathy, Focal Segmental Glomerulosclerosis and Membranous Nephrotic Syndrome

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Abstract

Long term outcome of 124 Thai adult nephrotic patients was determined. Nephrotic syndrome affects the young more often than the old (median age 29 years). The most common pathology was IgM nephropathy (45.2%), membranous nephropathy (31.5%) and FSGS (23.4%). Sixty four per cent of patients with IgM nephropathy respond to corticosteroid within 4-8 weeks while twenty three per cent were late responders. However, more than half of these patients were relapsers or steroid dependent. Response to corticosteroid occurred in 48.2 per cent of patients with FSGS while the response rate of patients with membranous nephropathy was only 23.1 per cent. Survival analysis revealed that five and ten years renal survival of IgM nephropathy was 98 per cent. Five and ten years renal survival of FSGS was 83.7 per cent and 76.8 per cent while those of membranous nephropathy was 95 per cent and 63.3 per cent. The response to corticosteroid was associated with better prognosis in FSGS. Our results show that patients with IgM nephropathy and membranous nephropathy have a generally good prognosis. Renal function is usually well preserved for at least ten years. The prognosis of patients with FSGS varied and correlated with the degree of steroid responsiveness.

Key word : Nephrotic Syndrome, Steroid Responsiveness, Renal Survival, IgM Nephropathy, Thai Ethnic

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Nephrotic Syndrome (NS) is one of the most common problems seen in out patient renal clinics in Thailand. Mesangial proliferative glomerulonephritis with IgM deposit (IgM nephropathy) was the most common pathological finding of these patients[1,2]. The latter can be considered a variant of minimal change disease. Interestingly, this high incidence of minimal change variant differs from the histologic spectrum found in Western countries. Unsatisfactory response to corticosteroid was first reported in Caucasians with Mesangial IgM glomerulonephritis[3]. This was not confirmed by later studies[4-6]. O' Donoghue found that the prognosis of IgM associated with mesangial proliferative disease was associated with initial histopathologic severity[7]. This led to a necessity to study the survival analysis of Thai patients with IgM nephropathy and compare it with that of another histologic subgroup. We, therefore, examined the prognosis of our nephrotic patients according to the degree of steroid responsiveness and renal pathology. Renal survival of each subgroup was assessed and compared.

MATERIAL AND METHOD

The medical records of all adult patients with primary nephrotic syndrome who were biopsied in our unit and had their last follow-up during the previous seven years were examined. All had edema, proteinuria > 3.5 g/day, serum albumin < 3.0 g/dl and serum cholesterol > 300 mg/dl. Patients with IgM nephropathy (Ig MN), focal segmental glomerulosclerosis (FSGS) and membranous nephropathy (MGN) were identified. No evidence of secondary nephrotic syndrome or systemic disease was found in the studied patients. All patients were initially treated with high dose (1 mg/kg/day) oral prednisolone. Treatment beyond the initial period was determined by the clinical responses and renal pathology. Patients were classified according to the degree of proteinuria at eight weeks and at last follow-up. This allowed a classification of clinical profiles as follows:

1. Steroid responders (SR): Patients who finally had complete remission (negative or trace dipstick proteinuria) or partial remission (proteinuria < 1 g/day). These patients were subclassified as initial or late responders if clinical remission was seen within or after 8 weeks. Some late responders had received concomitant treatment with cyclophosphamide.

2. Steroid nonresponders (SNR): Patients who finally did not have complete or partial remission (proteinuria > 1 g/day) after treatment and follow-up period of at least six months.

3. Relapsers: Steroid responsive patients who had recurrence of proteinuria after cessation of steroid therapy for at least one month. These patients were subclassified as frequent relapsers (two or more episodes of relapse within six months) or infrequent relapsers (less than two episodes of relapse within six months).

4. Steroid dependence: Patients who had recurrent of proteinuria during steroid tapering or had recurrence of protienuria within one month after cessation of steroid therapy.

The long term prognosis was evaluated by assessment of renal function. "Renal failure" was defined as doubling of serum creatinine to a value at least 2.5 mg/dl during the follow-up period. "End Stage Renal Disease" was defined as a stage when uremic symptoms developed or when dialysis was started. Renal survival was determined by Kaplan-Meier survival estimates. Comparison of survival between group was done by Log rank test.

Diagnosis of membranous glomerulonephritis (MGN) was based on WHO classification[8]. Geographical variation in the terminology of the idiopathic nephrotic syndrome were defined as follows:

IgM Nephropathy (Ig MN): A pathology of minimal change by light microscope with diffuse mesangial and, occasionally, paramesangial capillary wall deposit of IgM.The light microscope pathology may have mesangial matrix expansion or mild mesangial cell proliferation[9].

Focal Segmental Glomerulosclerosis (FSGS): A pathology of segmental and/or global glomerulosclerosis which affected some but not all glomeruli. Hyalinosis was often found in the capillary lumen adjacent to or in the sclerotic area. Immunofluorescent study revealed segmental deposit of C3 and IgM in sclerotic area. Mesangial IgM deposit may or may not be seen.

RESULTS

One hundred and twenty four patients were included. Sixty five were females and fifty nine were males. Patients were predominately young to middle aged. Mean ages were 33.63 ± 12.68 years with a median age of 29 years. The

Table 1. The number and renal pathology of patients according to the steroid responsiveness.

	N	Initial responders	Late responders	Non responders
Ig MN	56	36 (64.3%)	13 * (23.2%) 1 **	7 (12.5%) 1 **
FSGS	29	9 (31%)	5 (17.2%) 1 **	15 (51.7%) 7 **
MGN	39	6 (15.4%)	3 (7.69%) 2 **	30 (76.9%) 5 **
Total	124	51 (41.1%)	21 (16.9%)	52 (41.9%)

N.B. * includes 2 patients with spontaneous remission
** numbers of patients who have renal failure (doubling of serum creatinine)

mean and standard deviation of follow-up duration was 68.22 ± 62 months (range 6-286 months). No patients had minimal change pathology without mesangial IgM deposit. There were 56 IgM nephropathy, 29 FSGS and 39 MGN. Mean ages of membranous patients (40.69 ± 15.36 years) was significantly higher than that of Ig MN and FSGS (30.41 ± 12.19 years; $p < 0.05$). Clinicopathological profiles of each group were as follows:

1. IgM nephropathy (n = 56): Sixteen of these fifty-six patients did not have significant mesangial proliferation but had diffuse mesangial IgM deposit. The remaining 40 patients had both mesangial proliferation (more than 3 cells per area)[9] and diffuse mesangial IgM deposit. All had no superimposed focal and segmental sclerosis. Table 1 shows that 36/56 (64.3 %) of IgM nephropathy patients were initial responders (had partial or complete remission within 4-8 weeks). Another 11 (19.6%) were late responders (had partial or complete remission at the mean period of 23.4 3 ± 8.46 weeks; median 20 weeks). Among the 47 patients who were steroid responders, 19 (40.4%) were nonrelapsers and 28 (59.5%) were infrequent relapsers or steroid dependent. Mean prednisolone dosage for the 11 late responders was 22.14 ± 20.17, 11.66 ± 9.3 and 11.25 ± 8.3 mg/day at 16, 24 and 36 weeks respectively. Six of these late responders received concomitant cyclophosphamide at the dose of 75 ± 28.86 mg/day for 11 ± 1.41 weeks. Two further patients had spontaneous remission at 116 and 300 weeks with a maintenance prednisolone of 10 mg/day. The last seven patients (12.5%) were steroid nonresponders (SNR). One SNR died of septicaemia and renal failure during the period of high dose corticosteroid therapy for massive proteinuria. The remaining six SNR still maintained normal renal function at last follow-up. One steroid responsive patient developed doubling of serum creatinine (without proteinuria) at 188 months but did not develop end stage renal disease.

2. FSGS (n = 29): Nine patients (31.0%) were initial responders. Five additional patients were late responders (had remission at the mean period of 34 ± 13.66 weeks; median = 32 weeks). This led to a total remission rate of 48.2 per cent. Two of these five late responders received concomitant cyclophosphamide at the dose of 50 mg/day for 8 and 24 weeks respectively. Mean prednisolone dosage of these 5 patients was 18.3 ± 2.88, 11.66 ± 7.63 and 8.13 ± 2.39 mg/day at 16, 24 and 36 weeks. Fifteen patients (51.7%) were steroid nonresponders (SNR). Seven of the SNR had doubling of serum creatinine during the follow-up period. Three of them eventually developed ESRD. One late responder had acquired resistance and had doubling of creatinine but still did not progress to end stage renal disease.

3. MGN (n = 39): Six patients (15.4%) had partial remission within 4-8 weeks. Another 3 patients (7.69%) were late responders (had partial or complete remission at the mean period of 26 ± 8.48 weeks). This led to a total remission rate of 23.1 per cent. The rest 30 (76.9%) were SNR. Five SNR finally developed doubling of creatinine. One of them had ESRD. Two late responders had acquired resistance and eventually had doubling creatinine but still did not reach end stage renal disease. The pathological classification, response to treatment and incidence of renal failure are summarized in Table 1.

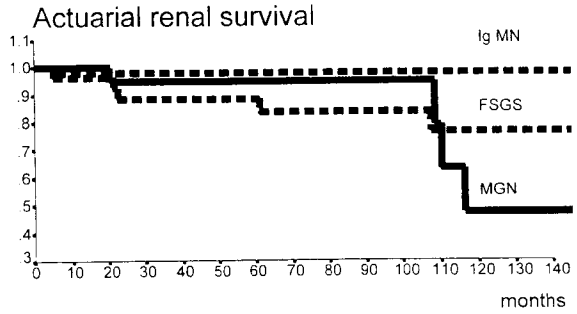

Fig. 1. Comparison of acturial renal survival between IgM nephropathy (n = 56), FSGS (n = 29) and MGN (n = 39).

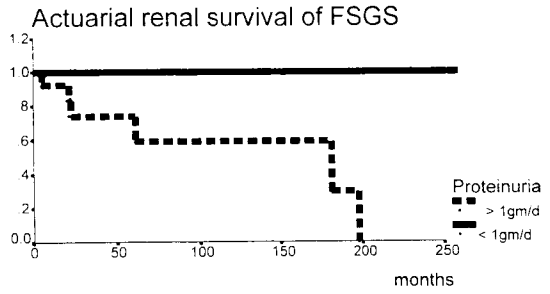

Fig. 2. Subgroup analysis of FSGS patients, comparing the acturial renal survival according to the magnitude of final proteinuria.

Fig. 1 compares the renal survival of all patients. Actuarial five year renal survival was 83.8 per cent, 95 per cent and 98.0 per cent for FSGS, MGN and IgM nephropathy respectively. The corresponding actuarial ten year renal survival was 76.8 per cent, 63.3 per cent and 98.0 per cent. FSGS had poorer five and ten year survival than IgM nephropathy ($p = 0.039$, Log rank test). MGN also had poorer five and ten years survival than IgM nephropathy ($p = 0.006$, Log rank test). Patients with MGN progressed to renal failure slower than FSGS. Subgroup analysis revealed that the prognosis of FSGS was also correlated with degree of steroid responsiveness. Fig. 2 shows the significant better renal survival of FSGS patients who were steroid responders when compared with nonresponders ($p = 0.007$, log rank test).

DISCUSSION

Frequent association of mesangial IgM deposit in Thai patients with nephrotic syndrome has been confirmed by several centers[1,2,10,11]. We have shown that response to steroid therapy was slow in our patients with Ig MN. However, after extended therapy, only 12.5 per cent of our patients with Ig MN were steroid nonresponders (Table 1). The high rate of steroid responsiveness was comparable with that of other studies of adult onset minimal change disease[12-14] but was different from other studies of glomerulonephritis with diffuse mesangial IgM deposit[3,7]. However, the proportion of our patients with Ig MN who were steroid dependent or relapsers were relatively high (59.5%). Of particular note was the relatively good renal survival of all patients with IgM nephroapthy. Even patients who were steroid nonresponders almost all maintain normal renal function at the ten year period. Our observation reflects that steroid nonresponsiveness may not necessarily be associated with poor renal outcome in Thai patients with IgM nephroapthy. Morbidity and mortality in adult onset MCNS was shown to be higher in the old rather than the young patients[13]. The relatively young age of our patients may thus be a factor which lead to good prognosis in our patients with IgM nephropathy.

The treatment response rate of our FSGS patients was much better than the results reported before 1980[15] but was comparable to later studies [16,17]. Banfi et al[18] showed that an extended period of steroid therapy, with or without alkylating agent, may be beneficial in some cases of FSGS. Our study provides evidence that Thai patients with FSGS who had reduction of proteinuria after an initial trial of corticosteroid should have a chance to receive extended therapy until the maximum benefit is achieved. The median time to achieve remission in our FSGS patients was 32 weeks. This was comparable with that derived from the study of Rydel et al[17] (5.5 ± 4 months). Of particular note is the trend towards increased favourable response with prolonged therapy that was observed

only in our patients with IgM nephropathy and FSGS but not membranous nephropathy. The mechanism of proteinuria of MCNS and FSGS are not completely known. Presence of circulating vascular permeability factor (s) was shown in some studies of MCNS and recurrent FSGS[19-21]. The benefits of prolonged therapy in our nephrotic patients may be related with suppression of vascular permeability factors. However, this notion still remains to be further clarified.

Due to the difficulties in comparing the benefits of several treatment regimens, most of our membranous patients were treated by an initial trial of high dose prednisolone and subsequent tapering if no favourable response was achieved. The renal survival was reasonably good up to a period of 10 years (Fig. 1). A prospective trial needs to be done to confirm whether a combination of methylprednisolone and chlorambucil will result in an excellent ten year survival in our membranous patients as has been reported in Caucasians[22].

An interesting observation from our study was the finding that four of our steroid responsive patients (1 Ig MN, 1 FSGS and 2 MGN) had either acquired resistance or doubling serum creatinine at long term follow-up. Other investigators[23,24] also observed this. This emphasizes that the prognosis of patients with nephrotic syndrome should be assessed by both the degree of steroid responsiveness and serial assessment of renal function.

In conclusion, we have shown that the renal survival of Thai patients with IgM nephropathy is generally good. The renal survival of membranous nephropathy was also good up to a period of ten years despite a low rate of steroid responsiveness. Five years renal survival was worse in FSGS than Ig MN and membranous nephropathy. The probability of renal failure of patients with FSGS can be predicted by the degree of steroid responsiveness. Our findings thus emphasize that renal biopsy provides useful information concerning the prognosis of patients with idiopathic nephrotic syndrome. This together with the result of survival analysis should be used as a guide to design optimum immunosuppressive therapy for each individual patient.

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การวิเคราะห์รอดชีพของผู้ป่วยไทยที่ป่วยด้วยโรค IgM nephropathy, Focal Segmental Glomerulosclerosis และ Membranous Nephrotic Syndrome

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ได้ติดตามผลการรักษาระยะยาวของผู้ป่วยเชื้อชายไทยที่ป่วยด้วยกลุ่มอาการเนโฟรติกและได้รับการตรวจทางพยาธิวิทยาจำนวน 124 ราย พบว่าผู้ป่วยส่วนใหญ่จะมีอายุไม่มาก (ค่าเฉลี่ยอายุเท่ากับ 29 ปี) พยาธิสภาพที่พบบ่อยคือโรคไตอักเสบชนิดที่มีไอจีเอ็มสะสมหรือ IgM nephropathy (45.2%), พยาธิสภาพที่พบบ่อยรองลงมาคือ membranous nephropathy (31.5%) และ FSGS (23.4%) 64% ของผู้ป่วย IgM nephropathy ตอบสนองต่อสเตียรอยด์ภายใน 4–8 สัปดาห์และผู้ป่วยอีก 23% ตอบสนองต่อสเตียรอยด์เมื่อให้การรักษายาวนานขึ้น อย่างไรก็ตาม มากกว่าครึ่งหนึ่งของผู้ป่วยเหล่านี้จะเป็น relapser หรือ steroid dependence อัตราการตอบสนองต่อสเตียรอยด์ในผู้ป่วย FSGS เท่ากับร้อยละ 48.2 ส่วนผู้ป่วย Membranous nephropathy ตอบสนองต่อสเตียรอยด์เพียงร้อยละ 23.1 ผลการวิเคราะห์รอดชีพพบว่าการอยู่รอดของไตที่ห้าและสิบปีของผู้ป่วย IgM nephropathy อยู่ในเกณฑ์ดีมาก (98%) อัตราการอยู่รอดของไตที่ห้าและสิบปีของผู้ป่วย FSGS เท่ากับ 83.7% และ 76.8% ส่วนอัตราการอยู่รอดของไตที่ห้าและสิบปีของผู้ป่วย Membranous nephropathy เท่ากับ 95% และ 63.3% ผู้ป่วย FSGS ที่ตอบสนองดีต่อสเตียรอยด์จะมีการพยากรณ์โรคดีกว่ากลุ่มที่ไม่ตอบสนอง การศึกษานี้แสดงให้เห็นว่าการพยากรณ์โรคของผู้ป่วย IgM nephropathy และ Membranous nephropathy อยู่ในเกณฑ์ดีมาก เพราะระดับการทำงานของไตมักจะไม่ลดลงมาก ส่วนการพยากรณ์โรคของผู้ป่วย FSGS มีความหลากหลายมากแต่สามารถคาดคะเนได้จากการตอบสนองต่อสเตียรอยด์

คำสำคัญ : กลุ่มอาการเนโฟรติก, การตอบสนองต่อสเตียรอยด์, การวิเคราะห์รอดชีพของไต, โรคไตอักเสบที่มีไอจีเอ็มสะสม, เชื้อชาติไทย

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