Primary Focal Segmental Glomerulosclerosis: Clinical Course, Predictors of Renal Outcome and Treatment

Hideo Shiiki and Kazuhiro Dohi

Abstract

Primary focal segmental glomerulosclerosis (FSGS) is the representative of refractory nephrotic syndrome in both adults and children. We review the clinical course and predictors of renal outcome in adult FSGS. Patients resistant to treatment frequently develop end-stage renal disease (ESRD), whereas patients achieving a remission show an excellent outcome. The renal survival rate in Japanese patients is 68.7% in 10 years and 31.4% in 20 years, indicating a better prognosis compared with the previous studies. When clinical and histological features at presentation have been evaluated by multivariate analysis, serum creatinine concentrations (>1.5 mg/dl) and the presence of tubulo-interstitial lesions (>20%) are significant positive predictors of progression to ESRD. We also discuss treatment for adult FSGS, with emphasis on intensive and prolonged therapy. (Internal Medicine 39: 606-611, 2000)

Key words: focal segmental glomerulosclerosis, prognosis, predictors, treatment

Introduction

Primary focal segmental glomerulosclerosis (FSGS) is a clinicopathological entity defined by the segmental sclerosis involving glomeruli in a focal distribution, and by the presence of massive proteinuria. The majority of patients with FSGS manifests nephrotic syndrome, while the minority shows mild to moderate proteinuria. Hematuria, hypertension and renal insufficiency are often seen at presentation (1, 2). Since the initial description of FSGS in 1957 by Rich (3), FSGS is generally believed to be steroid resistant, to have persistent nephrotic syndrome (refractory nephrotic syndrome), and to carry a poor prognosis (4). The recent advances in treatment with immunosuppressive drugs seem to improve the prognosis of FSGS in adults (5, 6). Nevertheless, except for tubulo-interstitial lesions, there are no reliable clinical or histological features at presentation that allow nephrologists to predict the response to therapy and renal outcome (7).

This article details the clinical course and possible prognostic predictors of FSGS in adults. We will also discuss the issues related to treatment and diagnosis.

Long-term Outcome

Previous studies demonstrated a 10-year renal survival rate of approximately 50% for nephrotic patients with primary FSGS (8-10). The most important finding is that the prognosis for nephrotic patients is dependent on the response to treatment irrespective of age at onset (5, 8, 11-13). Indeed 60 to 70% of patients resistant to treatment develop end-stage renal disease (ESRD) after 5 to 10 years. However, patients in remission show a favorable outcome, i.e. no more than 10% of patients progress to ESRD. A sustained remission carries a good prognosis, whereas recurrence of nephrotic syndrome may indicate a poor prognosis similar to primary non-responders (9, 11). Relapse is seen in only 15% of adult patients, in comparison to 80% in children (14). Most patients re-enter a remission regardless of age (12, 14).

An interim report of the Research Group on Progressive Renal Diseases in Japan (15) has shown a similar tendency in 221 adult patients with FSGS who developed nephrotic syndrome between 1983 and 1993, although the prognosis for Japanese patients seems to be more favorable than that for white and black patients. Ten-year and 20-year renal survival rates for all patients are 68.7% and 31.4%, respectively. More than 60% of patients who did not respond (including incomplete remission II) progressed to ESRD within 10 years, whereas less than 10% of patients achieving complete remission or incomplete remission I progressed to ESRD in 10 years (Fig. 1).

Predictors of Renal Outcome

As mentioned above, the response to therapy is critical in forecasting the probable course and prognosis of patients with FSGS. It is, therefore, desirable for nephrologists to be able to predict the response prior to therapy as well as eventual renal
Focal Segmental Glomerulosclerosis

The degree of proteinuria at presentation has been regarded as one of the most important indicators (8–10, 16). Patients with massive proteinuria (>14 g/24 h) had a malignant course with ESRD occurring within 6 years (9, 17). Interestingly, patients with non-nephrotic FSGS carried a more favorable outcome, i.e., a 10-year renal survival rate of over 80% (8–10). However, several recent studies did not support that amount of proteinuria at presentation influences the response to treatment (6, 18, 19). Renal dysfunction at onset appears to be related to a poor renal survival (9, 10, 16). Wehrmann et al (16) reported that patients with an elevated serum creatinine level (more than 1.3 mg/dl) show a significantly poorer outcome than those with a serum creatinine level ≤1.3 mg/dl. However, Banfi et al (12) have demonstrated that renal dysfunction at onset is not associated with the clinical course of adult FSGS. We also found no correlation between renal function at presentation and the response to therapy (19). This difference may be derived from the cause of renal dysfunction. Some patients show a transient renal insufficiency due to hemodynamic changes, while other patients already have irreversible histological damages, such as interstitial fibrosis and severe glomerular sclerosis. Other presenting features including age, sex, and presence of hypertension and hematuria are now thought to show no correlation with prognosis. As for hypertension, it is now believed to be an important factor in the progression of glomerulonephritis (6, 20). However, hypertension at presentation of FSGS has not been found to be of prognostic significance (12, 14, 19), suggesting that hypertension at presentation is induced by hemodynamic changes, not by permanent histological changes.

Controversy exists whether race influences the outcome of disease. Ingulli and Tejani (21) demonstrated that 78% of black children with FSGS progressed to ESRD compared to only 33% of white children. However, in the study of nephrotic adults by Korbet et al (10), no significant racial difference was observed in the prevalence of ESRD.

Histological features

In practice, renal biopsy findings are important for the prediction of prognosis in primary glomerulonephritis. However, with the exception of the presence of tubulo-interstitial lesions consisting of interstitial fibrosis and tubular atrophy, there appears to be no reliable histological marker of prognostic significance in FSGS (7). Earlier studies demonstrated that a percentage of global sclerosis and segmental sclerosis involving greater than 20% to 30% of glomeruli is an ominous sign (11, 22). However, several recent studies have revealed the opposite result, i.e., the percentage of segmental sclerosis and global sclerosis is not related to prognosis (7, 18, 19).

There is controversy regarding the significance of mesangial hypercellularity. Some studies demonstrated poorer prognosis in patients presenting with mesangial hypercellularity (23, 24), others revealed no correlation with outcome (9, 25). Recently, Ponticelli et al (6) have reported that mesangial proliferation was significantly correlated with renal failure in adults who underwent prolonged treatment with corticosteroids or immunosuppressive drugs.

As for location of segmental sclerosis within the glomerulus, three types have been categorized to evaluate renal outcome. The “hilar” type is characterized by segmental sclerosis linked to the glomerular hilum (vascular pole) (18). The “peripheral” type is defined as segmental sclerosis affecting peripheral tufts devoid of hilar involvement (18). The “tip” lesion originally reported by Howie and Brewer (26) is a special type of peripheral lesion located in the vicinity of the tubular pole occasionally consisting of foam cells and an adhesion. There is controversy whether hilar involvement of segmental sclerosis affects prognosis. In children, Ito et al (18) first reported worse prognosis for patients with the hilar type compared with the peripheral type. In contrast, subsequent other studies performed in children and adults have shown inconclusive results (7, 27, 28). Patients with the tip type are initially thought to have a better prognosis and response to therapy than usual cases. However, a follow-up study by Howie and Brewer (29) failed to confirm their previous findings. Our observation also disclosed no prognostic value in the position of segmental sclerosis in adults (19). Furthermore, serial renal biopsies occasionally exhibited transition from the peripheral or tip type to the hilar type (28), suggesting that the peripheral or tip type may be only an early lesion in the evolution of FSGS.

The cellular lesion of FSGS consists of proliferation, hypertrophy, vacuolization, protein re-absorption droplets, and separation from the glomerular basement membrane in the epithelial cells overlying the glomerular sclerosis (30). This lesion is also the hallmark of collapsing glomerulopathy that is
predominantly observed in black and that rapidly progresses to ESRD (31). Although several studies demonstrated poorer renal outcome in patients with the cellular lesion (31, 32), it remains to be settled whether collapsing glomerulopathy is a clinicopathological entity or whether the cellular lesion merely represents an early stage in the evolution of primary FSGS.

Until now, the severity of interstitial fibrosis consistently does predict a poor prognosis in primary FSGS (7, 16, 19). The significance of tubulo-interstitial changes in the prognosis of various types of glomerulonephritis also has been demonstrated in several studies (33, 34). Furthermore, several studies using multivariate analysis have confirmed importance of tubulo-interstitial changes (6, 7, 19). The percentage of segmental sclerosis and global sclerosis do not influence renal outcome as mentioned above. However, it is postulated that tubulo-interstitial changes depend on the glomerular lesions in primary glomerulonephritis (35). It is, therefore, speculated that a portion of tubulo-interstitial lesions may develop independently of the glomerular lesions of FSGS (16, 19).

Glomerular hypertrophy has been suggested to be one of the most important factors in the pathogenesis of FSGS (36, 37). Indeed, we have found that glomerular hypertrophy precedes the development of glomerular sclerosis in primary FSGS and is reversible when patients are in remission (38). However, few studies were conducted to examine relationship between prognosis and glomerular hypertrophy. Nyberg et al (39) showed that the glomeruli of steroid-dependent and steroid-resistant patients were larger than those of the steroid-responsive children. We also studied 35 adults with FSGS and found that the mean glomerular diameter was independently related to a significant risk of no response (19). Further larger studies are necessary to elucidate relationship between prognosis and glomerular hypertrophy.

Predictors in an interim report of the Research Group on Progressive Renal Diseases in Japan

The Research Group on Progressive Renal Diseases in Japan attempted to determine useful prognostic indicators using Cox’s proportional hazard models. Univariate and multivariate analysis for clinical features revealed that only a serum creatinine level ≥1.5 mg/dl was associated with a significant risk of progression to ESRD (relative risk, 3.30; 95% confidence interval, 1.09–10.02). Renal survival rate showed no correlation with age, sex, amount of proteinuria, serum concentrations of blood urea nitrogen or total cholesterol, and the presence of hypertension or hematuria. In renal biopsy findings, percentage of global sclerosis, percentage of segmental sclerosis, severity of tubulo-interstitial lesions, presence of vascular lesions, and location of segmental sclerosis were examined. In agreement with previous studies, the severity of tubulo-interstitial lesions occupying ≥20% of biopsy specimen was the only predictor for a poor prognosis in multivariate analysis (relative risk, 5.29; 95% confidence interval, 1.46–19.21), although univariate analysis showed correlation between percentage of global sclerosis and segmental sclerosis and prognosis.

Treatment of FSGS in Adults

Although many studies have been reported on FSGS, there are few randomized controlled clinical studies; most reports are case series with or without controls. Thus, there is limited evidence about the treatment of FSGS.

Generally speaking, the first approach for nephrotic patients with FSGS consists of high-dose prednisolone (0.5 to 2 mg/kg/day) for 2 months (40). The complete remission rate by steroid therapy has improved remarkably since 1980, and ranges from 30 to 60% of adults, whereas the response to steroid therapy was extremely poor prior to 1980 and reported complete remission rate was less than 20% (5, 41). The recent increase in complete remission appears to correlate with increased duration of steroid therapy, often with 5 to 8 months (5). In several studies, the mean time to remission takes 3 to 4 months (10, 12, 14). Therefore, steroid therapy should continue as long as possible in order to recognize the few responders (40). Burgess (42) recommended that steroid therapy must be given for at 6 months. The results of the Research Group on Progressive Renal Diseases in Japan are similar, and 37% and 21% of patients had complete remission and incomplete remission, respectively, with steroid therapy alone.

The use of cytotoxic therapy (cyclophosphamide, azathioprine, and chlorambucil) is now considered as second-line therapy (42). One-third of patients have received cytotoxic drugs along with steroids (5). Cytotoxic drugs with or without steroids induced complete remission in 30 to 60% of patients (5, 42). The complete remission rate is the same as that reported in the Research Group on Progressive Renal Diseases in Japan. Therefore, the percentage of patients in complete remission was not significantly different between steroids and cytotoxic drugs. However, Banfi et al (12) reported usefulness of prevention of relapse; only 18% of patients receiving alkylating drugs in addition to steroid relapsed compared with 55% of patients treated only with steroids.

Cyclosporin A (CyA) has been used in the treatment of both children and adults with FSGS for over 10 years. CyA is thought to be effective in reducing urinary protein excretion, although the number of randomized controlled drug trials has been very limited (43–45). Relapse after reducing the dose or stopping CyA is very common and nephrotoxicity of CyA is well known (46, 47). In 66 patients (11 adults and 55 children) with frequently relapsing or steroid-resistant nephrotic syndrome caused by minimal change nephrotic syndrome (MCNS) or FSGS, the effects of cyclophosphamide therapy (2.5 mg/kg/day for 8 weeks) were compared with CyA therapy (5 mg/kg/day for 6 months) in a randomized study (44). Complete remission was observed in about 2/3 of patients in both groups. Nevertheless, renal function was more stable in the cyclophosphamide group. In this context, Catran et al (48) have reported a randomized trial of CyA in 49 adults with steroid-resistant FSGS. CyA (3.5 mg/kg/day for 26 weeks) was administrated with low-dose steroids. Complete or partial remission rate was significantly higher in the CyA group than in the placebo group.
Focal Segmental Glomerulosclerosis

(70% vs. 4%, respectively). Renal function was better preserved in the CyA group. Relapse occurred in 60% of the remitters. Taking these results into consideration, CyA should be used for steroid-resistant FSGS irrespective of a high relapse rate and potential renal injury. Long-term use may be required to maintain remission (42, 48).

The use of angiotensin-converting enzyme inhibitors (ACEIs) has remarkably increased in the treatment of patients with various renal diseases irrespective of presence of hypertension. ACEIs are often prescribed for adult FSGS with expectation to decrease intraglomerular pressure and to inhibit interstitial fibrosis as observed in experimental glomerulonephritis (6, 48). Several small studies in patients with primary glomerulonephritis including FSGS demonstrated that ACEIs reduce proteinuria by approximately 30% (49-51). In a recently published prospective placebo-controlled study, patients with renal insufficiency caused by various renal diseases were treated with benazepril (52). The renal survival was significantly improved by benazepril. However, patients with a serum albumin level below 2.5 g/dl or with edema resistant to therapy were not included. Thus far, in FSGS with severe nephrotic syndrome there is no proven evidence for a positive long-term effect of ACEIs. Angiotensin II receptor antagonists may produce similar effects.

The use of low density lipoprotein (LDL) apheresis in the treatment of FSGS has been proposed to remove plasma LDL which may participate to the progression of FSGS (53). Although the usefulness of LDL apheresis has been reported in limited number of patients with FSGS (54), there are no results available concerning the long-term outcome.

The concept that the circulating “factors” lead to a glomerular permeability change for proteins in FSGS resulted in plasmapheresis trials of transplanted patients with recurrent FSGS (55, 56). Plasmapheresis has been used successfully to decrease proteinuria and to interrupt the progression of renal insufficiency in recurrent FSGS (55, 57). However, it remains to be clarified whether or not plasmapheresis is effective in patients with primary FSGS.

In agreement with Ponticelli et al (6), we do recommend intensive and prolonged treatment for adults with FSGS to achieve complete or incomplete remission (19). The treatment protocol we use is shown in Fig. 2. Prednisolone is initially prescribed to all patients at a starting dose of 40 to 60 mg p.o., daily for 4 to 8 weeks, with administration of anti-platelet drugs (dipyridamole 150 to 300 mg p.o., daily or dilazep 300 mg p.o., daily). When patients show resistance to steroid therapy, immunosuppressive therapy is initiated. Before 1996, we added cyclophosphamide (50 to 100 mg p.o., daily for 4 to 8 weeks) or mizoribine (150 mg p.o., daily for 3 to 6 months) without reducing the dosage of prednisolone. Since 1996, we have substituted CyA (3 to 5 mg/kg p.o., daily for 3 to 6 months) for cyclophosphamide or mizoribine. At least 2 kinds of immunosuppressive drugs are alternately used. If patients still show resistance to therapy, we continue to administer a moderate dose of prednisolone (15 to 20 mg p.o., daily) for more than 6 months, and usually for more than 1 year. In this protocol, 12 of 35 patients (34%) with nephrotic FSGS were in complete remission and 11 (31%) were in incomplete remission I or II, NR: no response.

**Figure 2.** Treatment protocol of FSGS with nephrotic syndrome. Dotted lines indicate the different possible options. CR: complete remission, ICR: incomplete remission I or II, NR: no response.

**Diagnostic Problems in FSGS**

The distinction between primary FSGS and MCNS presents a serious problem in evaluating the renal biopsy specimen, because the lesion of segmental sclerosis may not be present in specimens obtained due to the biopsy sampling. Indeed, a total number of glomeruli less than 10 does not seem to be a useful exercise, and reservations regarding the sampling error are certainly present. Conventionally, the presence of tubulo-interstitial scarring leads nephrologists to search carefully for FSGS, while mild changes have been reported in patients with MCNS (58). However, severe tubulo-interstitial lesions are also seen in some vascular diseases. We emphasize that alterations of glomerular epithelial cells and glomerular hypertrophy are useful histological markers for segmental sclerosis. The alterations...
of glomerular epithelial cells include hypertrophy, vacuolation, and numerous hyaline droplets (32). From our experience, the presence of glomeruli with a diameter larger than 220 μm is suggestive of FSGS; usually the glomerular diameter of patients with MCNS is less than 200 μm (unpublished data). When nephrologists and pathologists observe these changes, serial sections should be prepared in order to thoroughly search for segmental sclerosis.

In case of non-nephrotic FSGS, diagnosing is often more difficult than in nephrotic FSGS, because segmental sclerosis is one of the most common and non-specific patterns of glomerular injury encountered in renal biopsies. Of course, secondary FSGS caused by reflux nephropathy, obesity, hypertension, drug abuse and so on is easy to be excluded. However, like nephrotic FSGS, minor abnormalities and mesangial proliferative glomerulonephritis are often difficult to differentiate from primary FSGS when the number of glomeruli included in biopsy materials is insufficient. Recently, we have found a subgroup of non-nephrotic FSGS accompanied by both glomerular hypertrophy and increased numbers of glomerular capillaries (more than mean +2SD in normal controls) (59). Tubulo-interstitial changes are less prominent than those seen in reflux nephropathy. Therefore, one must keep non-nephrotic FSGS in mind if these two histological changes are observed in renal biopsies.

Conclusions

At almost 40 years after the original description of FSGS, controversies still remain about the response to therapy and predictors of renal outcome. To elucidate these problems, the Research Group on Progressive Renal Diseases in Japan conducted a nationwide retrospective survey of adults with primary FSGS. This study revealed a better renal survival rate compared with previous reports, an elevated serum creatinine and the presence of tubulo-interstitial lesions as significant positive predictors of ESRD, and the achievement of remission as a significant negative predictor of ESRD. However, usefulness of each treatment was not evaluated because of its retrospective nature. Controlled clinical trials concerning initial therapy and steroid-resistant FSGS are needed.

References

Focal Segmental Glomerulosclerosis