Renal Failure

ISSN: 0886-022X (Print) 1525-6049 (Online) Journal homepage: informahealthcare.com/journals/irnf20

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To cite this article: Mayuri Trivedi, Amit Pasari, Arpita Roy Chowdhury, Anila Abraham & Rajendra Pandey (2015) Tip variant of focal segmental glomerulosclerosis: is it truly a benign variant?, Renal Failure, 37:5, 763-768, DOI: 10.3109/0886022X.2015.1014755

To link to this article: https://doi.org/10.3109/0886022X.2015.1014755

Published online: 27 Feb 2015.

RENAL FAILURE

http://informahealthcare.com/rnf
ISSN: 0886-022X (print), 1525-6049 (electronic)

Ren Fail, 2015; 37(5): 763–768
 DOI: 10.3109/0886022X.2015.1014755

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CLINICAL STUDY

Tip variant of focal segmental glomerulosclerosis: is it truly a benign variant?

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Abstract

Background: Even though frequently described as a benign entity, the outcomes of the tip variant of focal segmental glomerulosclerosis (FSGS) have proven to be unclear. *Methods*: This retrospective study includes a cohort of tip variant cases who presented to us from 2009 to 2012 and the analysis of their presenting clinical, histopathological features and treatment outcomes in comparison to the not otherwise specified (NOS) variants from our center in East India. *Results*: Of the 224 biopsies of primary FSGS, 30 cases were the tip variant (13.39%). The mean age of presentation was around 29 years, with 57% being males. A nephrotic presentation was seen in 87% of cases, with 20% showing a presentation at <18 years of age for the first time. Global sclerosis, interstitial fibrosis, tubular atrophy and arteriolar hyalinosis were seen more commonly in the NOS variant. Twenty five patients of tip variant received steroid therapy and eight received alternative immunosuppression. Around 87% of the tip variant cases achieved some form of remission in proteinuria and 13.3% had a doubling of creatinine at a median follow-up of 2 years in comparison to NOS group in which 80% achieved some form of remission and 20% had a doubling of creatinine. *Conclusion*: Though the histopathological features and treatment responsiveness of the tip variant appear to be better than the NOS variety, the prognostic outcome does not seem to be as favorable as implicated previously with an important percentage of patients showing progressive worsening of renal function within a relatively short time span (2 years) in our cohort.

Keywords

Focal segmental glomerulosclerosis, India, nephrotic syndrome, NOS variant, tip variant

History

Received 29 August 2014
Revised 4 January 2015
Accepted 12 January 2015
Published online 27 February 2015

Introduction

Primary focal segmental glomerulosclerosis (FSGS) is a clinicopathological syndrome that is characterized by proteinuria of varying severity along with typical histopathological findings of focal and segmental scarring of the glomeruli.[1–3] It was first described by Rich in an autopsy series and has proven to be a common cause of nephrotic syndrome among both the pediatric and adult population.[1–4] It is also a common cause of chronic glomerulonephritis, which eventually progresses to end stage renal disease (ESRD) over a period of 5–10 years in 50% of the patients.[5,6]

Various histological variants of FSGS have been described in the past and attempts have been made to co-relate the long-term outcomes of patients with the histopathological variant.[1,7–10] The Columbia classification of primary FSGS has defined and classified the variants into five subtypes including (1) collapsing, (2) tip lesion, (3) cellular, (4) hilar and (5) not otherwise specified (NOS).[1,7] Various studies have proved that the histological variants do have a significant impact on the long-term outcome of the patient.

The tip lesion variant of FSGS has been believed to show a benign course and a relatively favorable long-term outcome.[11] It is defined by the presence of at least one segmental lesion involving the tip domain with either adhesion between the tuft and bowman's capsule at the tubular lumen or neck, or confluence of podocytes with parietal or tubular epithelial cells, at the tubular lumen or neck without perihilar or collapsing lesions and remains to have an unclear clinical significance.[7] It has been postulated that this lesion is the response of the glomeruli to heavy proteinuria and cases with this subtype of FSGS with no other lesion on histopathology may actually represent a form of minimal change disease (MCN).[12–14] However, there have been various studies which have shown that despite the histopathological similarities to the benign MCN the clinical course of the disease is similar to that of primary FSGS.[9,15,16]

Hence with the aim to study the clinical and histopathological features and the natural history and response to therapy of this variant of FSGS, we retrospectively reviewed our cases of primary FSGS and the tip lesion variant and compared the clinical and biochemical parameters as well as

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outcome of these patients with those of a relatively common histological variant of NOS.

Materials and methods

This is a single center retrospective data analysis. All native kidney biopsies diagnosed as FSGS between June 2009 and June 2012 were revised for cases with the tip variant and included in the study. The cases included had no history or other conditions to suggest secondary FSGS and had been classified as primary FSGS. The renal biopsies were confirmed by the same renal pathologist and were processed for light microscopy (LM) and immunofluorescence (IF). LM was carried out using H&E, Periodic Acid-Schiff (PAS), Silver Jones and Trichrome stains. IF was carried out using polyclonal FTIC antibodies to IgG, IgA, IgM, C3, C1q, kappa and lambda chain and graded as per the intensity of staining from 0 to 3. The percentage of glomeruli with segmental sclerosis (SS), global glomerulosclerosis (GS) and interstitial fibrosis and tubular atrophy (IFTA) was quantified. Inclusion criteria were the presence of at least one segmental lesion involving the tip domain by identifying the origin of the proximal tubule, without perihilar or collapsing lesion as previously described.[7] The clinical records of all the cases were reviewed and relevant baseline demographic, clinical and laboratory information as well as follow-up data were retrieved. The information included the gender, age, blood pressure, protein quantification and creatinine and estimated glomerulofiltration rate (eGFR), serum albumin, urine routine examination and serum cholesterol at presentation. eGFR was calculated using the modified diet in renal diseases study equation (MDRD) in adults and Schwartz equation in children (<18 years). At the end of follow-up, creatinine, eGFR, proteinuria and outcomes were registered.

Patients, in who complete data at presentation or last follow-up, were unavailable or had a follow-up for less than 9 months were excluded from the study. Also those who had an inadequate sample on renal biopsy (<5 glomeruli) were excluded as this was the minimum number chosen in previous published data.[8,16] Other glomerular pathologies which were in the past described to cause a tip variant like lesion (i.e. IgA nephropathy) were excluded. Standard therapeutic regimens and response to therapy definitions as well as outcome of disease were used.[17] Complete remission was defined as a 24 h urine protein level $\leq$300 mg/day with normal renal function and a partial remission was defined as 24 h urine protein $\geq$300 mg/day but $\leq$3 g/day with normal renal function.

Steroids were the initial choice of drug in all the patients. Steroid resistance or dependence or unacceptable toxicity to the drug was an indication for starting Tacrolimus or mycophenolate mofetil as second line therapy.

Statistical analysis

Data were expressed as mean $\pm$ SD or where indicated as median and ranges. Chi square test was used for categorical variables and Mann–Whitney test was used for continuous data. p-Values < 0.05 were considered statistically significant. All analyses were done using SPSS® software version 17.0 (SPSS Inc., Chicago, IL).

Results

Among the total number of native kidney biopsies, 224 biopsies were confirmed to be of primary FSGS. Thirty cases confirmed to be the tip variant (13.39%), 167 cases to NOS (74.5%), 14 cases to perihilar (6.25%), eight cases to cellular (3.57%) and five to the collapsing variant (2.23%). The patients with sub-nephrotic proteinuria at presentation were followed-up and treated with immunosuppression only when they progressed to nephrotic range proteinuria. Statistical analysis was not performed for the perihilar, cellular and the collapsing variants due to their relatively small numbers.

Demographic and initial clinical presentation data

The mean age of presentation of the tip variant was slightly more as compared to the NOS with almost similar number of patients who had a pediatric presentation (<18 years) of disease. Males were slightly more common in the NOS group (60.47%) as compared to the tip variant (56.6%) (Table 1).

The most common presentation in both groups was nephrotic range proteinuria, the tip variant showing 87% ($n = 26$) cases and NOS showing 88% ($n = 148$) cases presenting with similar degree of proteinuria at the initial presentation.

There was no statistically significant difference in the presenting features of hematuria, hypertension, renal

Table 1. Demographic and clinical presentation data.

Characteristics	FSGS NOS	Tip variant	p Value
Total numbers (n)	167	30	
Age at presentation (years)	28.42 $\pm$ 16.31	33.2 $\pm$ 15.02	0.106
Age <18 years at presentation	42 (25.1%)	6 (20%)	0.649
Hypertension	74 (44.3%)	12 (40%)	0.69
Renal dysfunction at presentation	89 (53.2%)	16 (53.3%)	1.0
Initial requirement for RRT	9 (5.3%)	2 (6.6%)	0.67
Serum creatinine (mg/dL)	1.59 $\pm$ 1.16	1.45 $\pm$ 0.6	0.63
eGFR (mL/min/1.73 m^2)	55.38 $\pm$ 24.45	50.95 $\pm$ 21.36	0.28
Serum albumin (mg/dL)	1.99 $\pm$ 0.56	1.94 $\pm$ 0.53	0.52
Serum cholesterol (mg/dL)	350 $\pm$ 99.2	319 $\pm$ 105.1	0.10
24 h urine protein (g/day)	5.89 $\pm$ 3.14	7.72 $\pm$ 6.51	0.27
Initial steroid therapy	160 (95.8%)	25 (83.3%)	0.021
Alternative immunosuppression	35 (21.8%)	8 (32%)	0.47
Median follow-up (months)	25 (9–30)	24 (9–26)	0.17

dysfunction (eGFR <60 mL/min) or the initial requirement of renal replacement therapy (RRT). Also the laboratory parameters were comparable in both groups.

Histopathological data

The total number of glomeruli in both the groups were comparable with the tip variant (17.6 ± 8.26) and the NOS (17.89 ± 7.8) for light microscopy (Table 2). The NOS variant showed a significantly higher number of lesions as compared to the tip variant with regards to the global sclerosis. Higher segmental sclerosis was seen in the tip variant though not statistically significant. Presence of arteriolar hyalinosis was not statistically different in the two groups; however, there was a complete absence of severe hyalinosis in the tip variant. Similarly, the presence of IFTA was similar in both groups with severe IFTA (>50% of core) being completely absent in the tip variant.

Follow-up and outcome

In the NOS group at the median follow-up of 25 months (range 9–30 months) 20.3% of patients showed a doubling of creatinine (Table 3). Among those who did not show progressive worsening of renal function, the NOS group showed complete remission in 57.8% of patients and partial remission in 42.1% patients. In the tip variant at the median follow-up of 24 months (range 9–26 months) while 13.3% of patient showed a doubling of creatinine, in those who did not, complete remission was seen in 80.76% of patients and partial remission in 19.2% patients. Thus though, the number of patients who achieved remission (complete or partial) was much higher in the tip variant ($p = 0.029$), the number of patients with progressive worsening of renal functions and also the requirement for alternative immunosuppression was not statistically different in the two variants ($p = 0.21$).

Drug therapy and response

All the patients included in this study had a minimum follow-up of 9 months (Table 4). In the NOS group, 160 patients (95.8%) received steroids as initial therapy, out of which 35 patients (21.8%) required alternative immunosuppression subsequently, which included 30 patients receiving tacrolimus and eight patients receiving mycophenolate mofetil (MMF). Three patients who received MMF following initial course of steroids were subsequently given tacrolimus due to lack of response to MMF and worsening proteinuria. In the tip variant group steroids were used in 25 patients (83.3%) initially out of which eight patients (32%) required alternative immunosuppression and subsequently received tacrolimus.

Table 4. Comparative outcomes between the tip variant and NOS groups based on the drugs used.

Treatment	NOS (%)	Tip variant (%)
Steroids (total)	160	25
Complete remission	97 (60.6)	18 (72)
Partial remission	42 (26.2)	5 (20)
Resistance	21 (13.1)	2 (8)
Tacrolimus (total)	30	8
Complete remission	8 (26.6)	3 (37.5)
Partial remission	16 (53.3)	5 (62.5)
Resistance	6 (20)	0
Mycophenolate mofetil (total)	8	0
Complete remission	0	0
Partial remission	5 (62.5)	0
Resistance	3 (37.5)	0

Table 2. Comparative features in renal histopathology.

Characteristics	NOS	Tip variant	*p* Value
No. of patients	167	30	
Average no. of glomeruli	17.8 ± 7.8	17.6 ± 8.26	0.9
Glomerular (% of total glomeruli)			
Global sclerosis	12.74 ± 17.8	5.93 ± 13.90	0.02
Segmental sclerosis	22.95 ± 21.32	26.36 ± 27.32	0.72
Vascular (%)			
Mild	24 (14.37%)	1 (3.3%)	
Moderate	12 (7.18%)	2 (6.6%)	0.096
Severe	5 (2.9%)	0	
Tubulointerstium			
No IFTA	116 (69.46%)	26 (86.66%)	
<25% IFTA	28 (16.76%)	3 (10%)	
25–50% IFTA	21 (12.57%)	1 (3.33%)	0.075
>50% IFTA	2 (1.1%)	0	
Acute tubular injury	13 (7.7%)	2 (6.66%)	1.0

Table 3. Final outcome of tip variant group as compared to NOS group.

Final outcome	NOS ($n = 167$)	Tip variant ($n = 30$)	*p* Value
Progressive worsening of renal function (doubling of serum creatinine)	34 (20.3%)	4 (13.3%)	0.214
Normal renal functions	133 (79.6%)	26 (86.6%)	
1. Complete remission	77 (57.8%)	21 (80.7%)	0.029
2. Partial remission	56 (42.1%)	5 (19.2%)	

Table 5. Comparative features based on age of onset in tip variant group.

Characteristics	Age <18years	Age >18 years	p Value
Numbers	6	24	
Hypertension	2	10	1.0
Serum creatinine (mg/dL)	0.76 ± 0.12	1.63 ± 0.55	<0.001
eGFR	79.33 ± 6.28	43.85 ± 17.44	<0.001
Glomeruli with global sclerosis (%)	0	7.39 ± 15.25	0.065
Glomeruli with segmental sclerosis (%)	19.51 ± 5.53	27.31 ± 29.7	0.56
IFTA	1	3	1.0
Arterial hyalinosis	0	3	1.0
Need for alternative immunosuppression	0	8	0.15
Complete remission	4	17	0.55
Partial remission	2	3	
Doubling of serum creatinine	0	4	1.0

In order to gain insight into the behavior of these variants in the pediatric onset and adult onset subgroups we analyzed the cohorts further and compared the two subsets within each cohort (Table 5). When the adult subgroup of tip variant and NOS variant was compared statistical significant differences were observed in the adult cohort with the NOS variant showing more severe involvement on histopathology with higher percent of glomeruli showing segmental ($p = 0.011$) as well as global sclerosis ($p < 0.0001$). Also this cohort showed worse serum creatinine ($p < 0.0001$) and eGFR ($p < 0.0001$) at presentation with significantly higher requirement for alternative immunosuppression ($p = 0.032$) as compared to the adult population of the tip variant group. The analysis within each variant comparing the childhood onset and adult onset subgroups yielded no significant difference in the presenting features, histopathology or the outcomes except a significantly higher need for alternative immunosuppression in the adults as compared to children of the NOS group and the adults showed a significantly worse presenting creatinine and eGFR ($p < 0.001$) as compared to the children within the tip variant.

Discussion

Idiopathic FSGS has been described as a disease that encompasses a pathologically diverse group of patients with distinctive demographic characters, clinical and laboratory features and ultimate outcomes. We compared the demographic characteristics, presenting features, natural history and the outcome of the tip variant of FSGS with that of the NOS group. The patients with the tip variant presented at an older age (4th–5th decade) in our cohort as compared to the NOS group (3rd–4th decade) and also as compared to the previously described literature which found the tip variant to be seen in the teenage more frequently.[8,16,18] This may be considered as an ethnic variation seen in our population from the Indian sub-continent. However, there was no difference in distribution of patients who showed a pediatric onset (20%) and adult onset of this disease (80%) in the two groups. We observed that in our patients of the NOS group even though the evidence of injury to the glomeruli in the form of global glomerulosclerosis was higher; their age of presentation was lesser as compared to the tip variant thus negating the effects of age related glomerular scarring. The tip variant did have a comparable incidence of segmental lesions, IFTA and arteriolar hyalinosis as seen in the NOS lesion. Therefore, to consider the tip variant as just a ''footprint'' of heavy proteinuria would be inappropriate and it definitely merits its own significance as an independent subtype of FSGS. Also the NOS variant, as already known, has a more prolonged duration of nephrosis due to its less obvious proteinuria which may delay the diagnosis as compared to the tip variant which has a higher degree of proteinuria and therefore is diagnosed at an earlier stage due to the overt symptoms.[18]

Several reports in the past have shown an excellent response to steroid therapy in the tip variant with outcomes similar to the minimal change disease rather than FSGS.[12–15,24] However, it has also been shown that the overall behavior and ultimate outcome of this disease are more like FSGS as was seen in our study also.[9,20–22] The incidence of initial steroid responsiveness was higher in the tip variant with 72% of patients achieving complete remission after steroid therapy. However, the subsequent requirement of alternative immunosuppression in both groups was similar showing no statistically significant difference ($p = 0.47$). Similar results may be seen in the final outcome of the disease where even though the number of patients achieving complete or partial remission in the tip variant (89.6%) was significantly higher as compared to the NOS group (79.6%) ($p = 0.029$), however, the progressive worsening of renal functions was not statistically different in the groups ($p = 0.214$). Hence, we feel that the clinical significance of higher steroid responsiveness may not co-relate very well with the ultimate outcome and therefore the tip variant requires a more stringent follow-up despite its apparent excellent steroid responsiveness.

Thus, though traditionally the NOS variant has always been known to have a relative worse outcome as compared to the tip variant, our study shows that the tip variant can no longer be considered to be a favorable prognostic variant. In a study by Arias et al.[23] though 14.9% of patients belonged to the tip variant and had a significant less evidence of chronic damage on histopathology (GS, IFTA, AH), the overall prognosis was not favorable with 28% of patients progressing to CKD and 16% progressing to ESRD.

Howie and Brewer[15] had reported that in patients with glomerular tip lesions attaining complete remission with therapy, had an excellent prognosis with a 10 year survival of nearly 90% but in patients unresponsive to therapy, the renal survival was 30% which is the case in traditionally described

Table 6. Comparison between patients with tip variant who showed progressive worsening of renal functions versus those who had stable renal function.

Characteristics	Doubling of serum creatinine	Stable renal function	*p* Value
Number of patients	4	26	
Age (years)	52.5 ± 5.74	30.2 ± 13.7	0.002
Hypertension (*n*)	4 (100%)	8 (30.7%)	0.018
Creatinine (mg/dL)	1.59 ± 0.28	1.43 ± 0.64	0.27
eGFR (mL/min/1.73 m^2)	46.8 ± 8.55	51.5 ± 22.7	0.88
24 h urine protein (g/day)	3.97 ± 2.09	8.3 ± 6.78	0.005
Glomeruli with SS (%)	42.1 ± 41.3	23.2 ± 24.0	0.27
Glomeruli with GS (%)	27.0 ± 32.8	2.66 ± 3.56	0.35
IFTA (*n*)	1 (25%)	3 (11.5%)	0.45
Arteriolar hyalinosis (*n*)	1 (25%)	2 (7.69%)	0.36
Need for alternate immunosuppression	2 (50%)	6 (23.07%)	0.28

FSGS.[16] In a study by Stokes et al. the tip variant was found to have a behavior similar to MCD with only one patient out of 29 progressing to ESRD at the end of 21 months.[24]

In accordance with the published literature our study also showed a more aggressive nature of NOS patients with more severe chronic renal injury on histopathology as well as a worse presenting serum creatinine and eGFR. However, these features did not translate into a poorer outcome as compared with the tip variant which had similar rates of progressive renal injury. Thus, in our cohort of the patient the histological variant did not co-relate with ultimate outcome in both the groups.

Our study showed 13% of patients in the tip variant had a doubling of serum creatinine values with a median follow-up of 24 months as compared to 20% in the NOS group. Since we have a relatively shorter follow-up period (range 9–30 months) we preferred to consider doubling of creatinine as the end point as compared to progression to CKD or ESRD.

In our work we observed that the patients, who had a progressive worsening of renal functions, belonged to older age group ($p = 0.003$) and had hypertension ($p = 0.01$) more commonly (Table 6). Surprisingly 24 h urine protein at presentation was significantly higher in the patients who did not show a progressive deterioration ($p = 0.005$), which might have led to faster diagnosis and therapy intervention in them. Also these patients showed much higher global glomerulosclerosis, IFTA (25%) and arteriolar hyalinosis (25%) and steroid resistance (50%). However, this data failed to show any statistical significance which may be due to a relatively small number of patients (four patients with doubling of creatinine). Also the other limitation of our study and most other studies on this subject is the relatively short follow-up period.

Conclusion

The tip variant is an etiopathogenic and clinically different morphological variant of FSGS which has been described to have the most favorable prognosis with regards to renal survival with highest steroid responsiveness and less severe chronic renal damage on biopsy (global sclerosis, IFTA). However, the prognostic implications for this lesion do not appear to be as favorable as described earlier, with progressive renal injury being seen in an important percentage. We, therefore, feel that even though the overall prognosis of NOS lesion is worse, it is time to reanalyze the prognosis and outcome of the tip variant lesions in various ethnic groups and identify the factors associated with worse outcome in longer follow-up. Therefore, this variant requires rigorous follow-up and intervention with regards to the modifiable factors of disease progression.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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