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Subsequent Transition from Minimal Change Disease to Secondary form of Focal Segmental Glomerulosclerosis: Not a Sampling Error yet Still Amenable to Immunosuppressive Therapy

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Abstract

Background: Previous studies suggested that the focal and segmental nature of focal segmental glomerulosclerosis (FSGS) may lead to sample error or diagnosis error that results in minimal change disease (MCD) misdiagnosis, or FSGS being missed especially in patients with early lesions or limited glomeruli in the biopsy specimens. Patients and methods: Over the past 5 years, patients were included in the study if they had (a) relapse of nephrotic syndrome (NS), (b) biopsy-proven FSGS without immune deposits, (c) long-remission (years) after biopsy-proven Corticosteroid-refractory NS due to MCD, (c) negative history, clinical examination, radiological scans as well as laboratory and serological tests for autoimmune diseases, infections, malignancy and drugs-side effect. Results: After 3 months of therapy with Losartan alone; Proteinuria decreased only by 22% improvement with a mild decrease in Creatinine clearance (ClCr) by 1.5%. However, the addition of Mycophenolate mofetil (MMF) resulted in a further significant decrease in Pr to 72% compared to Losartan alone. Moreover, there were no significant changes in CrCl after 1- and 2 years of follow up. Our data indicates that such a transition may not be due to inadequate sampling but a new lesion. Initial hemodynamic therapy with Losartan was not adequate and immunosuppressive therapy with MMF significantly improved proteinuria and stabilized their kidney function. The data is promising with regard to the management of patients with such relentless disease. In conclusion, a true transition from MCD to FSGS is amenable to therapy with MMF.

Keywords

Corticosteroids, Focal Segmental Glomerulosclerosis, Minimal Change Disease, Mycophenolate Mofetil, Nephrotic Syndrome, Transition

1. Introduction

Idiopathic nephrotic syndrome (INS) is the most common form of nephrotic syndrome (NS) in children, accounting for > 90% of cases [1]. Its prevalence is nearly 16 cases per 100,000, yet its worldwide incidence varies widely between 1.2 and 16.9 cases per 100,000 children, varying by ethnicity and region [2]. The majority of children with INS respond to corticosteroids (C) with a reduction of mortality rate in childhood INS to around 3%, though infection remained the most common cause of death. Hence, kidney biopsy was limited only to the 70% of cases that manifest C-refractory and C-resistant cases to avoid their adverse effects such as obesity, poor growth, hypertension, diabetes mellitus, osteoporosis and adrenal suppression [3]. The distribution of histopathologic categories, among patients with INS, revealed that 76.6% had minimal change disease (MCD) and 6.9% had focal and segmental glomerulosclerosis (FSGS) [1]. Both disorders manifest severe and acute NS with variable responses to C. On a clinical basis, 90% of those with MCD exhibit C-responsiveness and/or C-refractoriness versus only 30% in FSGS [4]. The transition from MCD to FSGS is not rare in clinical practice [5] [6]. However, the focal and segmental nature of FSGS may lead to sample error or diagnosis error, which results in MCD misdiagnosis, or FSGS being missed especially in patients with early lesions or limited glomeruli in the biopsy specimens [7]. Such sampling error is commonly revealed by repeat kidney biopsy in those with subsequent C-resistance that shows segmental sclerotic lesions and IgM deposits on immune-stains and electron microscopy [8]. In our study, we describe a different group of patients in whom MCD disease abated for years yet to relapse gradually later in life with a lack of deposits both on immune-stains and electron microscopy indicating a true transition of a phenotypic MCD.

2. Patients and Methods

Over the past 5 years; patients were included in the study if they had; (a) relapse of NS, (b) biopsy-proven FSGS without immune deposits, (c) long-remission (years) after biopsy-proven C-refractory NS due to MCD, (c) negative history, clinical examination, radiological scans as well as laboratory and serological tests for autoimmune diseases, infections, malignancy and drugs-side effect.

2.1. Study Design

Initially, all patients were treated for 3 months with Losartan alone as well as a low

protein and sodium diet. The dose of Losartan was titrated up, from 50 to 100 mg, as tolerated and without hypotension. After the initial phase, Mycophenolate mofetil (MMF) was added till the end of the study.

2.2. Periodic Assessment

Patients were seen on monthly basis for 3 months then every 2 months subsequently. In those visits, patients were assessed clinically for severity and complications of their NS as well as side-effects of therapy. During those visits, laboratory investigations were done and included, complete blood count as well as serum estimates of sugar, renal, liver function tests, lipid profiles and urine routine. Twenty-four-hour urine collections for daily protein excretion (Pr) and creatinine clearance (CrCl)were done at times 0, 3 months, 6 months, 12 months, 18 months and 24-months.

2.3. Statistical Analysis

SPSS statistical package version 25 was used for data entry and processing. The p-value ≤ 0.05 was used as the cut-off level for significance. Since age, duration of previous NS-remission, duration of follow up, Pr and CrCl were normally distributed; they were expressed as mean ± SD. Comparison of changes in protein output and creatinine clearance with time, following therapy, was done by t-test for repeated measures.

3. Results

A total of 11 patients fulfilled the clinical criteria for inclusion in the study. Patient's demographical characteristics, their initial Pr and CrCl, after 3-month of Losartan-therapy alone and after 1- and 2-year therapy with Losartan and MMF combination are summarized in Table 1. Eight (73%) patients were males. All were adults with (age at 27 ± 4 years). Their duration of remission after previous was 113 ± 13 months and their duration of follow up was 41 ± 11 months.

3.1. Response to Therapy

As shown in Table 1, after 3-month therapy with Losartan alone; Pr decreased to 7073, representing a 22% improvement and CrCl decreased only by 1.5%. However, the addition of MMF resulted in a further significant decrease in Pr by 72% compared to Losartan alone. Moreover, there were no significant changes in CrCl after 1- and 2-year of follow up.

3.2. Side Effects of Therapy

Treatment with Losartan led to a mild decrease in CrCl, mild yet tolerable cough and shortness of breath in 2 patients, hyperkalemia yet controlled with diet alone in 4 patients. Addition of MMF was associated with abdominal pains and diarrhea that indicated lowering of their initial dose to 500 mg thrice daily.

Table 1. Demographical data and response to therapy in patients with FSGS following MCD.

Patients' characteristics		(n = 11)
Demographical data	Gender (F/M)	3/8
	Age (years)	27 ± 4
	Duration of NS remission (months)	113 ± 13
	Duration of follow up (months)	41 ± 11
Response to therapy with Losartan & MMF*	Time 0:	
	Proteinuria	9069 ± 837
	Creatinine clearance	67 ± 3
	Time 3 months	
	Proteinuria	7073 ± 895
	Creatinine clearance	66 ± 2
	Time 1 year	
	Proteinuria	2008 ± 299
	Creatinine clearance	66 ± 3
	Time 2 years	
	Proteinuria	1854 ± 280
	Creatinine clearance	64 ± 2

Abbreviations: MMF: Mycophenolate mofetil, FSGS: Focal segmental glomerulosclerosis, MCD: minimal change disease.
*Proteinuria expressed in mg/24 hours & creatinine clearance in ml/minute.
*Significant improvement in proteinuria ($p < 0.00001$) from time 0 to 3 months and 3 months to 1 year.
Moreover, significant improvement in proteinuria ($p < 0.00$) from 1 to 2 years.
However, creatinine clearance decrease between time 0 and 3 months ($p<0.01$) then not significant
between time 3 months and 2 years. Between 1 & 2 years; further mild decrease ($p < 0.2$).

4. Discussion

Primary FSGS and MCD are among the main causes of idiopathic nephrotic syndrome, termed as podocytopathies. Both manifest diffuse foot processes effacement, under electron microscopy, due to change in the adhesion molecules between glomerular basement membrane and the pedicel (defective actin cytoskeleton) [9]. The presumed etiology of primary ones is a T-cell induction of permeability plasma-factors viz. soluble urokinase plasminogen activator receptor (suPAR), cardiotrophin-like cytokine factor-1 (CLCF-1), and CD40 antibodies [10]. They affect different adhesion molecule between the podocyte and GBM, with resultant variable responsiveness to immunosuppressive therapy [10]. In contrast,

secondary forms of FSGS are associated with; (a) excessive nephron workload (hyperfiltration), due to maladaptation, associated with reduced nephrons, obesity, hypertension, and (b) direct glomerular injury due to high-penetrance genetic FSGS due to mutations in one of nearly 40 genes (familial FSGS), virus-associated FSGS, and medication-associated FSGS [11]. Moreover, emerging data support the identification of a sixth category: APOL1 risk allele-associated FSGS in individuals with sub-Saharan ancestry [8]. The pathogenesis of the primary podocytopathies, induced by such permeability factors, is best seen in recurrence of post-transplant FSGS which is not reported in secondary forms [12]. Our patients underwent kidney biopsy at the time of initial diagnosis of NS, which pathologically revealed only MCD. They did not exhibit, at that time and subsequently, clinical characters of missed FSGS viz. (a) steroid-resistance, (b) persistent proteinuria, hematuria and hypertension, as well as (c) progressive disease on follow up with that culminates ESKD [11]. Moreover, they did not have features of secondary or familial forms of FSGS associated with lack of IgM deposits in the sclerotic glomerular lesions. In our patient, the significant response to MMF, compared to ARB, indicates autoimmune disorder responsible for such transition despite a lack of glomerular immune deposits. In rodents, non-diabetic podocytopathies of MCD and FSGD were induced by a dose-dependent inducibles viz. passive Heymann nephritis, puromycin aminonucleoside nephrosis, adriamycin nephrosis, liopolysaccharide, crescentic glomerulonephritis, and protein overload nephropathy model [13]. The dose dependence of animal models supports the hypothesis that MCD and FSGS are two successive pathological processes of podocyte disease. Both models are based on the induction of podocytic injury and subsequent podocyte loss, with differences depending on the degree of podocyte injury and the severity of podocyte loss. Only the foot process of podocyte exfoliation similar to that in MCD is observed in the initial phase, while persistent podocyte loss results in the persistent damage leading to FSGS [13]. In the initial stages, this disease is steroid-sensitive. With relapses and delays, continuous proteinuria and podocyte loss lead to a decrease and/or loss of C-sensitivity. When podocyte loss is more than 30% - 40%, progressive damage and glomerular loss are inevitable [14]. Levels of integrins including α and β dystroglycan which determine the attachment of podocytes to basement membranes are low in C-sensitive MCD compared to C-resistant one and FSGS [15]. Our study explains the subsequent development of C-refractoriness and even resistance in MCD and also FSGS since such primary podocytopathy is an immune-mediated phenomenon with an escalating dose of podocytes-antigenemia.

Treatment should include more aggressive and potent antiproliferative agents such as MMF. It has 3 advantages: (a) it is a potent immunosuppressive agent, even in corticosteroid-resistant glomerulonephritis and organ transplants, (b) its safe long-term oncogenicity and gonadal toxicity compared to Cyclophosphamide, and (c) its antiproliferative effect which limits future glomerulosclerosis and progressive kidney disease [16] [17]. Limitations of the study include; its limited

number of patients and lack of long-term follow up. However, it is the first to disclose such an uncommon glomerulopathy and provides means of diagnosis, management and short- as well as medium-term follow up.

5. Conclusion

Late transition from true MCD to FSGS can develop as an escalating dose-dependent autoimmune podocyte injury and is amenable to therapy with MMF.

Author's Contributions

Prof/Kamel El-Reshaid conceived the study, participated in its design, and drafted the manuscript. Dr. Shaikha Al-Bader and Hossameldin Tawfik Sallam participated in the study design, follow up of patients and data collection and tabulated the data. Dr John Madda participated in the study design, and was responsible for histological diagnosis, data collection and tabulation of histological data.

Data Availability Statement

The data provided in the current review are available from the references.

Conflicts of Interest

All authors have read and approved the final version of the manuscript. The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] International Study of Kidney Disease in Children (1978) Nephrotic Syndrome in Children: Prediction of Histopathology from Clinical and Laboratory Characteristics at Time of Diagnosis. *Kidney International*, **13**, 159-165. https://doi.org/10.1038/ki.1978.23

[2] Noone, D.G., Iijima, K. and Parekh, R. (2018) Idiopathic Nephrotic Syndrome in Children. *The Lancet*, **392**, 61-74. https://doi.org/10.1016/s0140-6736(18)30536-1

[3] Hodson, E.M., Knight, J.F., Willis, N.S. and Craig, J.C. (2004) Corticosteroid Therapy for Nephrotic Syndrome in Children. *Cochrane Database System Review*, **2**, CD001533.

[4] Tarshish, P., Tobin, J.N., Bernstein, J. and Edelmann, C.M. (1997) Prognostic Significance of the Early Course of Minimal Change Nephrotic Syndrome. *Journal of the American Society of Nephrology*, **8**, 769-776. https://doi.org/10.1681/asn.v85769

[5] Alshami, A., Roshan, A., Catapang, M., Jöbsis, J.J., Kwok, T., Polderman, N., *et al.* (2017) Indications for Kidney Biopsy in Idiopathic Childhood Nephrotic Syndrome. *Pediatric Nephrology*, **32**, 1897-1905. https://doi.org/10.1007/s00467-017-3687-3

[6] Ahmad, H. and Tejani, A. (2000) Predictive Value of Repeat Renal Biopsies in Children with Nephrotic Syndrome. *Nephron*, **84**, 342-346. https://doi.org/10.1159/000045609

[7] Wang, C. and Greenbaum, L.A. (2019) Nephrotic Syndrome. *Pediatric Clinics of North America*, **66**, 73-85. https://doi.org/10.1016/j.pcl.2018.08.006

[8] Rosenberg, A.Z. and Kopp, J.B. (2017) Focal Segmental Glomerulosclerosis. *Clinical Journal of the American Society of Nephrology*, **12**, 502-517. https://doi.org/10.2215/cjn.05960616

[9] Machado, J.R., Rocha, L.P., Neves, P.D.M.d.M., Cobô, E.d.C., Silva, M.V., Castellano, L.R., *et al*. (2012) An Overview of Molecular Mechanism of Nephrotic Syndrome. *International Journal of Nephrology*, **2012**, 1-6. https://doi.org/10.1155/2012/937623

[10] McCarthy, E.T., Sharma, M. and Savin, V.J. (2010) Circulating Permeability Factors in Idiopathic Nephrotic Syndrome and Focal Segmental Glomerulosclerosis. *Clinical Journal of the American Society of Nephrology*, **5**, 2115-2121. https://doi.org/10.2215/cjn.03800609

[11] Shabaka, A., Tato Ribera, A. and Fernández-Juárez, G. (2020) Focal Segmental Glomerulosclerosis: State-of-the-Art and Clinical Perspective. *Nephron*, **144**, 413-427. https://doi.org/10.1159/000508099

[12] Rudnicki, M. (2016) FSGS Recurrence in Adults after Renal Transplantation. *BioMed Research International*, **2016**, 1-7. https://doi.org/10.1155/2016/3295618

[13] Pippin, J.W., Brinkkoetter, P.T., Cormack-Aboud, F.C., Durvasula, R.V., Hauser, P.V., Kowalewska, J., *et al*. (2009) Inducible Rodent Models of Acquired Podocyte Diseases. *American Journal of Physiology-Renal Physiology*, **296**, F213-F229. https://doi.org/10.1152/ajprenal.90421.2008

[14] Maas, R.J., Deegens, J.K., Smeets, B., Moeller, M.J. and Wetzels, J.F. (2016) Minimal Change Disease and Idiopathic FSGS: Manifestations of the Same Disease. *Nature Reviews Nephrology*, **12**, 768-776. https://doi.org/10.1038/nrneph.2016.147

[15] Vogtlander, N.P.J., van der Vlag, J., Bakker, M.A.H., Dijkman, H.B., Wevers, R.A., Campbell, K.P., *et al*. (2009) Expression of Sialidase and Dystroglycan in Human Glomerular Diseases. *Nephrology Dialysis Transplantation*, **25**, 478-484. https://doi.org/10.1093/ndt/gfp465

[16] Sollinger, H.W. (2004) Mycophenolates in Transplantation. *Clinical Transplantation*, **18**, 485-492. https://doi.org/10.1111/j.1399-0012.2004.00203.x

[17] Stassen, P.M., Kallenberg, C.G.M. and Stegeman, C.A. (2007) Use of Mycophenolic Acid in Non-Transplant Renal Diseases. *Nephrology Dialysis Transplantation*, **22**, 1013-1019. https://doi.org/10.1093/ndt/gfl844