Clinico-pathological characterization of primary Steroid Resistant Nephrotic Syndrome in infants and children

Thesis

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Abstract

Steroid resistant nephrotic syndrome (SRNS) contributes disproportionately to end stage renal failure. Focal segmental glomerulosclerosis (FSGS) is the commonest histopathology described in primary SRNS. Studies reported clinical, laboratory and histopathological characteristics that would predict course and outcome. In this study, we studied the relation between clinico-laboratory parameters and renal histopathology in a cohort of Egyptian infants and children who had primary SRNS. The study included 51 cases, (14 infants and 37 children) with mean age of onset of 35±32.7 months. Features of glomerulonephritis were generally uncommon (less than 50%). Non-minimal change disease was found in 96% of our cases. FSGS was the main finding in patients with nephrotic syndrome in first year of life (NSFL) and childhood onset NS. Response to immunosuppressive medications was poor (3/37 achieved complete remission). In patients with NSFL, partial remission was detected in only one case. Cyclophsphamide was the commonest prescribed immunosuppressive. Sixteen of our cases deceased at mean age of 51.21 ± 40.4 months. The main cause of death was fulminant sepsis (12/16). Eight of these cases were on immunosuppression. In conclusion, patients with SRNS are most likely to have non-MCD with poor response to immunosuppression. No clinical, laboratory on imaging study could predict clinical course or outcome in these patients.

Key words:

Focal segmental glomerulosclerosis- Non-MCD- End stage renal failure- Resistance to immunosuppressive medications.

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List of abbreviations

ACEi:	**Angiotensin Converting Enzyme inhibitor**
AFP:	**Alpha Fetoprotein**
ATIII:	**Antithrombin III**
CNI:	**Calcineurin inhibitor**
CNS:	**Congenital nephrotic syndrome**
CPA:	**Cyclophosphamide**
CsA:	**Cyclosporine A**
DDS:	**Denys Drash Syndrome**
DMS:	**Diffuse Mesangial sclerosis**
EGORD:	**Egyptian Group of Orphan Renal Disease**
EM:	**Electron Microscopy**
ESRF:	**End stage Renal Failure**
FGGS:	**Focal global glomerulosclerosis**
FSGS:	**Focal segmental glomerulosclerosis**
GBM:	**Glomerular Basement Membrane**
GFR:	**Glomerular Filtration Rate**
IgA:	**Immunoglobulin A**
IGF1:	**Insulin related Growth Factor 1**
IGF2:	**Insulin related Growth Factor 2**
IgM:	**Immunoglobulin M**
INS:	**Idiopathic Nephrotic Syndrome**
ISKDC:	**International Study of Kidney Disease in Children**
KDIGO:	**Kidney Disease Improving Global Outcomes**
LM:	**Light Microscopy**
MCD:	**Minimal change disease**

List of abbreviations (continued)

MesPGN:	**Mesangial proliferative glomerulonephritis**
MN:	**Membranous nephropathy**
MPGN:	**Membranoproliferative Glomerulonephritis**
NFAT:	**Nuclear factor of activated T cell**
NOS:	**Not otherwise specified**
NS:	**Nephrotic syndrome**
NSFL:	**Nephrotic syndrome in the first year of life**
PNS:	**Primary nephrotic syndrome**
PTD:	**Proximal tubular dilatation**
SDNS:	**Steroid dependant nephrotic syndrome**
SNGFR:	**Single nephron glomerular filtration rate**
SRNS:	**Steroid resistant nephrotic syndrome**
SSNS:	**Steroid sensitive nephrotic syndrome**
TGF:	**Tumor growth factor**
VEGFa:	**Vascular endothelial growth factor**
WT1:	**Wilms Tumour suppressor gene 1**

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Introduction

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Introduction

Nephrotic syndrome (NS) is the most common glomerulopathy encountered in pediatric practice. It is defined by the presence of nephrotic-range proteinuria (protein in urine >1gm/m^2/day), edema, hypoalbuminemia and hyperlipidemia. It is characterized by altered perm-selectivity of the glomerular filtration barrier, ***(Gulati et al, 2009).***

The International Study of Kidney Disease in Children (ISKDC) demonstrated that clinical corticosteroid response had a high predictive accuracy for outcome than renal histological findings in children with idiopathic nephrotic syndrome. Hence, the practice of performing kidney biopsy at presentation in all children was abandoned and over the years the role of kidney biopsy has become more and more restricted, **(*Gulati et al, 2006).***

Between 10 and 20% of children with primary (idiopathic) nephrotic syndrome are steroid resistant (SRNS). The risk of primary steroid resistance depends on the initial histopathology, ***(Otukesh et al, 2009).***

In the kidney biopsy, SRNS is associated with the histological features of focal segmental glomerulosclerosis (FSGS) in approximately 75% of patients, whereas 20% demonstrate minimal change disease (MCD), ***(Büscher et al, 2012).*** Other renal histopathological findings in SRNS are mesangial proliferative glomerulonephritis (MesPGN), membranoproliferative glomerulonephritis (MPGN), immunoglobulin M (IgM) nephropathy, C1q nephropathy, IgA nephropathy and membranous nephropathy ***(Donadio et al, 2002*, *Myllymaki et al 2003, Niaudet, 2004b, Vizjak et al, 2008 and Alchi et al, 2010).***

Focal segmental glomerulosclerosis is the most common renal histopathology described in primary SRNS. In FSGS, sclerosis (a process defined by glomerular capillary collapse with increase in the matrix) involves some, but not all glomeruli (focal) and affects a portion but not the entire glomerular tuft (segmental). ***(Shi et al, 2007).***

Several pathologic variants of FSGS were investigated for their prognostic significance. The NOS (not otherwise specified) variant is the commonest morphologic pattern seen in primary FSGS, while the perihilar, cellular, tip and collapsing variants are less common. The activity score of the cellular and

collapsing variants is also higher than that of the other three variants. The cellular and collapsing variants are the patterns associated with active lesions, while perihilar variant is the pattern associated with chronic lesions. The tip variant shows mild pathological changes compared with the other patterns, ***(Shi et al, 2007).***

Mutations of NPHS1, NPHS2, or WT1 may be responsible for severe forms of nephrotic syndrome in children, progressing to end-stage renal failure, ***(Niaudet et al, 2004a).*** In addition to, Finnish type NS or diffuse mesangial sclerosis which are common in nephrotic syndrome in the first year of life and are clearly genetic disorders, ***(MacHardy et al, 2009)***.

Also, there is increasing information indicating a genetic basis for many cases of FSGS and that these would not be expected to respond to immunosuppressive medications, ***(Otukesh et al, 2009)***. Other genes may be involved in the slit-diaphragm or the nephrotic syndrome, ***(Antignac et al, 2005).*** A novel TRPC6 mutation that leads to early onset FSGS was recently mapped, ***(Heeringa et al, 2009).***

Steroid resistant nephrotic syndrome may be secondary to infections or systemic disorders, such as systemic lupus erythromatosis, hepatitis B virus infection and sickle cell disease. ***(Eric et al, 2009)***

Although SRNS represents a small fraction of all pediatric NS cases, it contributes disproportionately to end stage renal failure (ESRF), ***(McBryde et al, 2001)***. After a follow-up of 10 years, end-stage renal failure develops in 30–40% of children with SRNS, ***(Mendoza et al, 1990& Niaudet et al, 1997).***

Renal survival rates in SRNS vary somewhat based on the underlying histology but average 50–60% for children with idiopathic FSGS, ***(Cattran et al, 1998).*** Treatment has been directed against immunological abnormalities in SRNS using immunosuppressive agents. Supportive management comprises of, when indicated, therapy with angiotensin converting enzyme inhibitors and statins ***(Gulati et al, 2009).***

Aim of the work

The study was conducted to determine the clinical, biochemical and histopathological characteristics of primary SRNS in a cohort of Egyptian infants and children. We also aimed to study the correlation between clinico-laboratory parameters and renal histopathology in studied patients.

Review of literature