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Restrospective single-center study analysing type of primary nephrotic syndrome complicated by acute kidney injury

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ABSTRACT :

Introduction

Acute Kidney Injury (AKI) in primary nephrotic syndrome (NS) is a devastating condition if not diagnosed and treated early. AKI diagnosed in the context of the primary nephrotic syndrome might be due to several causes including acute tubular necrosis secondary to hypovolemia or sepsis, rapid progression of the native glomerular disease, acute interstitial nephritis (antibiotics, diuretics, nonsteroidal antiinflammatory drugs), and bilateral renal vein thrombosis. AKI in primary NS has been considered as a complication and MCD is considered benign for its abrupt onset and rapid recovery with emperical steroids but the underlying vulnerability to AKI is a subject of focus as no previous studies were done at this center.

Objectives

To analyse the incidence of acute kidney injury in primary nephrotic syndrome and to determine the types of primary Nephrotic syndrome complicated by AKI.

Materials and Methods

A retrospective single-center study was conducted with the histopathologically diagnosed 1001 primary NS patients, out of 3313 patients admitted, at the nephrology department of the first affiliated hospital of Zhengzhou University from January 2009 to July 2010 during residency period at Zhengzhou, China. The analysis of incidence of AKI among 1001 primary NS patients were done.

Results

The incidence rate of AKI in primary NS was 11.7%. Minimal change disease (55%) was the commonest type of primary NS complicated by AKI.

Conclusion

AKI occurred in 11.7% of primary NS patients in our cohort. The minimal change disease was the commonest type of primary NS that was prone to develop AKI.

Key words: Acute kidney injury, Primary nephrotic syndrome

INTRODUCTION

The nephrotic syndrome (NS) is a condition where massive proteinuria results in hypoalbuminaemia with hypercholesterolemia and oedema formation. Alteration in podocyte in nephrotic syndrome is associated with impairment in kidney function as nephrotic syndrome leads to increased susceptibility to infections, thromboembolism, altered lipid and carbohydrate metabolism, and losses of binding proteins in the urine.[1] According to the etiology, NS can be classified into primary and secondary NS. And the primary NS (PNS) is an exclusive diagnoses.

Acute Kidney Injury Network's (AKIN) diagnostic criteria for acute kidney injury (AKI) include an abrupt (within 48 hours) reduction in kidney function currently defined as an absolute increase in serum creatinine of ≥0.3 mg/dl (≥26.4 μmol/L), a percentage increase of ≥50% (1.5-fold from baseline), or a reduction in urine output (<0.5 ml/kg per h for >6 h).[2]

AKI is a serious complication of primary NS if not diagnosed and treated early. Causes included hypovolumia, rapid progression of the glomerular disease itself e.g. rapidly progressive glomerulonephritis (RPGN), endocapillary proliferative glomerulonephritis (EnPGN), acute interstitial nephritis (antibiotics, diuretics, nonsteroidal anti-inflammatory drugs), and renal vein thrombosis(RVT). Sometimes, PNS and AKI arised simultaneously

following treatment with drugs such as with nonsteroidal anti-inflammatory drugs (NSAIDs), diuretics. In other circumstances, AKI complicated pre-existing PNS in the absence of any of the above conditions.

AKI in the context of the primary NS presents a unique array of potential diagnoses. The epithelial cell injury, if severe, could trigger both nephrotic range proteinuria and acute or subacute renal failure.[3] This typically occured as a manifestation of a primary glomerular disease such as collapsing glomerulopathy or crescentic membranous nephropathy. Less dramatic visceral epithelial cell injury, in combination with proximal tubular injury (e.g., panepithelial cell injury induced by NSAIDs or possibly undiagnosed viral illness) or interstitial nephritis (e.g., antibiotics, NSAIDs induced) could also present as AKI complicating the NS.[4]

Acute tubular necrosis (ATN) in association with the nephrotic syndrome was seen in a subpopulation of older patients with minimal change disease.[3] Renal vein thrombosis (RVT) must always be considered in the differential diagnosis; however, the commonest cause for AKI in the patient with the primary nephrotic syndrome is thought to be the prerenal AKI complicating diuretic therapy for mobilization of edema.[5]

This study is focused on analysing incidence of AKI in primary NS patients and anlalysing histopathological types of primary NS complicated by AKI. Also, the literature is reviewed and the pathophysiological mechanisms for causes of AKI in primary NS along with a case report are discussed.

OBJECTIVES

- To analyse the incidence of acute kidney injury in primary NS
- To analyse the type of primary NS complicated by AKI.

METHODOLOGY:

A retrospective study done in clinically and histopathologically diagnosed 1001 primary NS patients with AKI, out of 3313 admitted at the nephrology department of the first affiliated hospital of Zhengzhou University from January 2009 to July 2010.

Method:

The following data were assessed: the clinical presentation and histopathological diagnosis of patients of primary nephrotic syndrome, and the clinical evidence of AKI present in those PNS patients. Clinical presentations were classified as follows: primary nephrotic syndrome (edema, proteinuria ≥ 3.5 g/24 h, hypoalbuminemia and hyperlipidemia)[1] and modified AKI definition was used.[2] (Increase in serum creatinine of >26.5umol/l within 48 hours). Blood sampling was done. The entry criteria were as follows: patient aged above 15 years had the diagnosis of idiopathic nephrotic syndrome, had follow-up for at least 3 months. Patients with lupus nephritis, hepatitis associated nephropathy, diabetic nephropathy, purpura nephritis, rapidly progressive glomerulonephritis with positive ANCA (anti-neutrophil cytoplasmic antibody titer) and anti-glomerular basement membrane antibody titer and secondary nephrotic syndrome were excluded.

Renal biopsies were usually done in the left kidney and 2 cores of cortical biopsy specimens were sent to renal pathology laboratory of nephrology department of the first affiliated hospital of Zhengzhou University where examination by renal pathologist in light microscoscope [after staining with hematoxylin and eosin(H & E), Masson's trichrome, impregnation with methenamine silver stain, Periodic acid-Schiff (PAS) stain], immunofluorescence microscope[anti-IgA, -IgG, -IgM, -C3, -C1q, -fibrinogen, -kappa and -lambda polyclonal antibodies conjugated with fluorescein isothiocyanate (Dako, Glostrup,Denmark)] and electron microscope were done. The histopathological diagnoses were obtained from the renal biopsy reports and among them the type of PNS complicated by AKI were studied.

RESULTS

From January 2009 to July 2010, a total of 3313 patients were admitted at nephrology department of first affiliated hospital of Zhengzhou University with biopsy confirmed 1001 cases of primary NS among which 117 cases of PNS were complicated by AKI. The incidence rate is as shown in Table 1.

Table 1: Incidence of AKI in PNS

Studied records of	Number of patients	Incidence rate (%)
Total patients	3313	
Primary NS	1001	30.21
AKI in PNS	117	11.7

Among 117 patients with AKI, male predominated with 72 cases (61.53%). Youngest patient was 19 years and oldest patient was 76 years. Types of PNS complicated by AKI were:

Table 2. Number of patients with histopathological types of PNS complicated by AKI

Types of PNS	MCD	MsPGN	MPGN	FSGS	MN	EPGN
Number of patients	65	22	15	11	3	1

Incidence rate of PNS complicated by AKI was 11.7%. The results of renal biopsies at our hospital were as follows:

Fig.1. Pie chart showing proportion of histopathological diagnosis of 1001 patients of primary nephrotic syndrome. [Abbreviation: MCD MCD=Minimal change disease, MsPGN=Mesangioproliferative glomerulonephritis, MPGN= membranoproliferative glomerunephritis, FSGS= focal segmental glomerulosclerosis, EnPGN= Endocapillary proliferative glomerulonephritis, MN= membranous nephropathy]

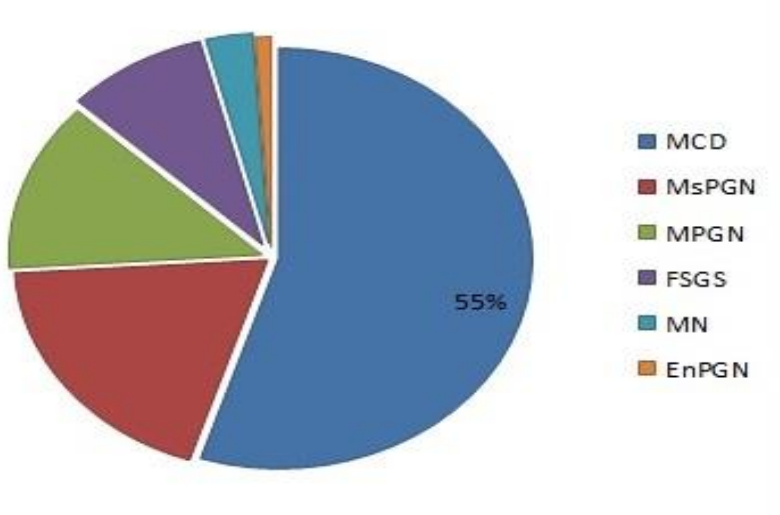

Fig.2 Pie chart demonstrating proportion of histopathological analysis of 117 cases of PNS patients complicated by AKI. [Abbreviation MCD=Minimal change disease, MsPGN=Mesangioproliferative glomerulonephritis, MPGN= membranoproliferative glomerunephritis, FSGS= focal segmental glomerulosclerosis, EnPGN= Endocapillary proliferative glomerulonephritis, MN= membranous nephropathy]

Typical slides in patients with PNS complicated by AKI in our hospital are as followings:

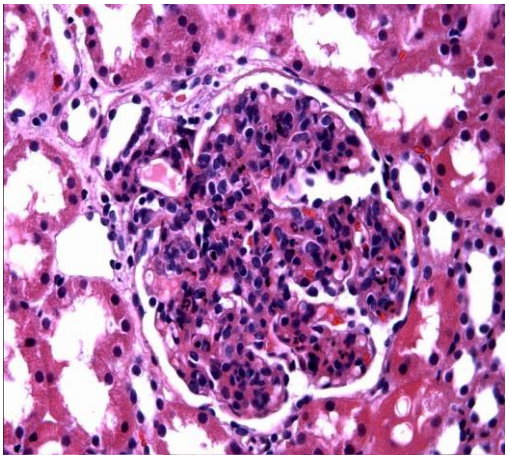

Fig.3 Hematoxylin and Eosin stain with Endocapillary hypercullularity[400X]

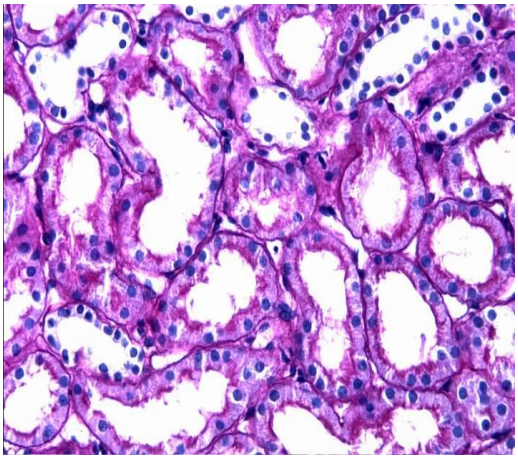

Fig.4. Periodic Acid-Schiff (PAS) stain in LM of Minimal Change disease[400X]

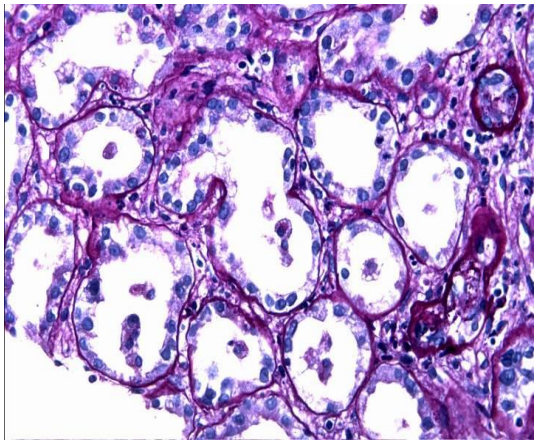

Fig.5 Acute tubular necrosis(ATN) with shedding of epithelial cells[400X]

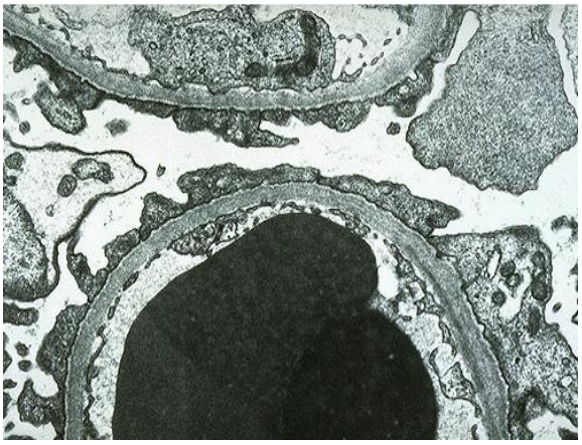

Fig.6 Electron microscopic view with diffuse effacement of podocyte foot processes[9420X]

DISCUSSION

MCD was the commonest (55%) type of PNS complicated by Acute kidney injury. AKI could occur in idiopathic MCD, and usually the glomerular filtration rate fully recover to baseline.[6]

Although many patients with MCD had a decrease in the glomerular filtration rate during the nephrotic phase that might be interpreted as "functional renal insufficiency", kidney function returns to normal following resolution of the nephrotic syndrome, even after multiple relapses.[7] In a series of 51 patients, 61 percent had higher than normal serum creatinine values when patients were actively nephrotic but renal function returned to normal when remission was achieved. [7] End-stage renal disease was rare, and had only been reported in steroid-resistant cases.[8] However, FSGS was often seen on late renal biopsy in patients with glucocorticoid-resistant or relapsing disease and in all patients who develop progressive renal failure. Whether this represents sampling error on the initial renal biopsy due to the focal nature of FSGS, or true progression from MCD to FSGS is uncertain.[9] So our study focused on type of NS complicated by AKI.

The incidence of AKI in primary NS is quite common (11.7%). It is not harmonius that MCD, with such an excellent prognosis for resolution of proteinuria and preservation of renal function, imparts some degree of renal insufficiency in 1% to 10%.[10, 11] In contrast to the paucity of glomerular lesions, Smith and Hayslett [[12]], in a review of severe, oliguric AKI in patients with idiopathic nephrotic syndrome, found "frequent and widespread abnormalities of the tubulointerstitium" suggestive of acute tubular necrosis in 39 of 65 biopsies, and the diagnosis of MCD was confirmed by renal biopsy in approximately 85% of the reported cases. The pathogenesis of AKI in MCD might be due to decreased glomerular filtration permeability resulting in decreased glomerular filtration rate as suggested by Robson et al.[13] The fact that massive proteinuria occurring in MCD despite impaired glomerular permeability is due to loss of charge selective barrier.[14] The complication of AKI in patients with MCD, especially when associated with acute interstitial nephritis, should prompt a careful search for an etiologic agent, such as nonsteroidal anti-inflammatory drugs (NSAIDs), which also may cause the glomerular lesion, or the concomitant administration of a potentially nephrotoxic drug, such as a diuretic, or agents that might cause interstitial nephritis. In these cases, the renal insufficiency was reversed by discontinuing the drug. None of our patients had exposure to such drugs and all patients were vitally stable without hypotension and with haematocrit within normal range. None of them had flank pain and evidence of RVT in renal biopsy.

The pathogenesis of AKI in the setting of MCD had several possible explanations. In adults with MCD, AKI was associated with older age and vascular disease, [13] but this association could not explain AKI in children, in whom hypertension was rare and chronic vascular disease was absent.

Although increased glomerular permeability exposes the tubular epithelium to injury by a variety of substances found in the filtrate, tubular necrosis related to proteinuria in itself seems unlikely in MCD because a high degree of selectivity excludes most potentially toxic substances from the filtrate. In most cases, the origins of tubular injury and dysfunction reside in the altered hemodynamics seen in patients with the nephrotic syndrome. It had been suggested that this form of tubular damage was the result of hypovolemia owing to low plasma oncotic pressure, but the absolute and relative blood volumes and the renal plasma flow were well preserved in most patients with the nephrotic syndrome.[11] Chen et al found that immunohistochemical staining for endothelin 1 (ET-1) was stronger in patients with MCD and AKI than in patients with MCD and normal renal function.[14] They hypothesized that the cytokines that are increased in MCD may induce ET-1 production. ET-1 may induce mesangial cell contraction, which may result in reduced filtration surface area and glomerular filtration rate and thus AKI. MCD patients with AKI showed good prognosis within 7 weeks after prompt treatment with corticosteroids. Clinically relevant biomarkers for AKI and soluble factors for MCD diagnosis and treatment monitoring will be helpful for noninvasive diagnosis and early treatment.

CONCLUSION

AKI occurred in 11.7% of primary NS patients in our cohort. The minimal change disease was the commonest type of primary NS that was prone to develop AKI.

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