Severe reversible acute renal failure in idiopathic nephrotic syndrome

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ABSTRACT

Background: Only few cases of acute renal failure (ARF) requiring dialysis have been reported in patients with idiopathic nephrotic syndrome (NS). This study aims to better define the clinical outcome and treatment of this condition.

Methods: A pilot enquiry regarding the occurrence of ARF requiring dialysis in patients with NS and biopsy proven minimal changes (MC) or focal segmental glomerulosclerosis (FSGS) was conducted among 5 nephrology centers.

Results: From 1996-2006, 6 patients with idiopathic NS (4 MC, 2 FSGS) developed ARF requiring dialysis early after onset of NS. At presentation all but 1 patient had elevated blood pressure. Patients were treated with dialysis from 7-40 days. All achieved complete or partial remission after 4-8 weeks of steroids. Recovery of renal function paralleled with the reduction of proteinuria. At renal biopsy proximal tubules showed a large amount of protein droplets, flattening of epithelial cells, and focal detachment of cells from the basal membrane. After a follow-up of 24-60 months, 5 patients had a relapse. Of these 4 were responsive to steroids, while one progressed to dialysis after an episode of hemolytic uremic syndrome related to cyclosporine treatment. ARF did not recur.

Conclusion: ARF requiring dialysis is a rare and unexpected complication of idiopathic NS occurring in most cases early after presentation. These patients are sensitive to steroids that should be administered as promptly as possible in view of the potential noxious effect of protein overload on proximal tubular cells.

Key words: Acute renal failure, Minimal changes nephrotic syndrome, Nephrotic syndrome, Proteinuria, Prednisone, Tubular necrosis

INTRODUCTION

Acute renal failure (ARF) is a rare complication of adult idiopathic nephrotic syndrome (NS). In 1992 Smith and Hayslett (1) reviewed the English literature on this topic and summarized the characteristics of 79 episodes occurring in 75 patients in whom the renal biopsy documented minimal changes (MC) in 85% and focal segmental glomerulosclerosis (FSGS) or mesangial lesions in the remaining patients. In most cases ARF developed early after onset of the first episode of NS, and recovered even after a prolonged period of severe oliguria or anuria spontaneously or concomitantly with steroid treatment. However, 14 patients died due to a complication of uremia or required chronic dialysis. Since then only a few similar cases have been reported as single case reports (2, 3) or in the context of a large series (4). The occurrence of ARF in idiopathic NS may be underrecognized especially in older adults. In a renal biopsy study of 259 patients with ARF aged >60, clinical diagnosis before biopsy, was not correct in 7/9 patients with NS who had a histological diagnosis of MC disease (5). Patients with idiopathic NS who develop ARF are characterized by severe proteinuria and a very low serum albumin concentration (1). Renal biopsy studies in these patients have focused on tubular lesions. Signs of acute tubular necrosis such as loss of brush border, flattening and simplification of proximal tubular cells and focal detachment of cells from the basement membrane were observed in 60% of cases (1). Not all studies however, used standardized criteria to describe acute tubular damage. In addition, clinical criteria to define ARF are not uniform and some series have included patients with mild renal dysfunction.

In order to better define the clinical and histological features and the outcome of this condition, we selected 6 patients...
with idiopathic NS who developed severe ARF requiring dialysis and were submitted to renal biopsy.

**PATIENTS AND METHODS**

**Subjects**

After a pilot enquiry among five nephrology centers around Milan, we identified 6 patients observed over a decade from 1996-2006 and fulfilling the following characteristics: a) full-blown NS, b) absence of systemic disease, malignancy, drug exposure, prolonged hypotension, c) ARF requiring dialysis developing concomitantly to the NS, d) renal biopsy performed immediately before or during the oliguric episode showing an histological pattern of MC or FSGF without extensive glomerular or interstitial involvement, e) a follow-up of at least 1 year.

**Definitions**

Complete remission: proteinuria <0.2 g/24h, estimated glomerular filtration rate (GFR) >60 ml/min per 1.73 m². Partial remission: proteinuria from 0.2 and 1 g/24h, estimated GFR >60 ml/min per 1.73 m². Relapse: proteinuria >3.5 g/24h in subjects who went in complete or partial remission of NS.

**Histopathology**

All renal biopsy specimens were adequate for light microscopy (at least 10 glomeruli) and immunofluorescence evaluation. Electron microscopy findings were available in 4 patients. Light microscopy findings were evaluated by two of the authors (EI and TS) who scored glomerular, tubular, interstitial and vascular lesions on a scale from 0 to 3+. Acute tubular injury was graded according to the presence and extension of tubular simplification, loss of brush border, cell necrosis and detachment from the basal lamina (6). Interstitial lesions were graded on the basis of the portion of cortical area affected and arteriolar changes on the basis of intimal thickening.

**RESULTS**

**Clinical characteristics**

All 6 patients developed ARF at the first episode of NS. In the past medical history arterial hypertension was present in 2 patients (n. 5 and n. 6), and was controlled with angiotensin converting enzyme (ACE) inhibitors and loop diuretics, although at presentation blood pressure (BP) was above the normal range in all but 1 patient (Tab. I). One patient (n. 2) was treated with mesalamine for ulcerative colitis and 1 patient referred seasonal allergic asthma episodes (n. 4). All patients denied the use of non-steroid anti-inflammatory drugs. All patients were oliguric and severely oedematous at presentation. Laboratory findings showed a high level of urinary protein excretion, marked hypoalbuminemia and hyper-cholesterolemia (Tab. I). Serologic markers of systemic disease were absent and C3 and C4 complement were normal. No abnormality was found at ultrasound investigation of the urinary tract. Signs of renal vein thrombosis were absent. Five patients were extremely oliguric and had severely reduced renal function at presentation before they were treated by loop diuretics. High dose furosemide was

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**TABLE I**

**CLINICAL CHARACTERISTICS AT PRESENTATION**

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age (years)</th>
<th>Gender M/F</th>
<th>Pre-existing HT</th>
<th>Time (d) - Dialysis*</th>
<th>sCr (mg/dL)</th>
<th>BP mmHg</th>
<th>Proteinuria g/d</th>
<th>Serum albumin g/dL</th>
<th>Days on dialysis</th>
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<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>M</td>
<td>-</td>
<td>40</td>
<td>1.6</td>
<td>145/80</td>
<td>15</td>
<td>2.1</td>
<td>13</td>
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<tr>
<td>2</td>
<td>58</td>
<td>M</td>
<td>-</td>
<td>5</td>
<td>6.1</td>
<td>170/115</td>
<td>10</td>
<td>2.1</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>73</td>
<td>F</td>
<td>-</td>
<td>12</td>
<td>5.3</td>
<td>170/90</td>
<td>10</td>
<td>2.3</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>44</td>
<td>M</td>
<td>-</td>
<td>3</td>
<td>5.7</td>
<td>170/100</td>
<td>5</td>
<td>2.0</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>66</td>
<td>M</td>
<td>+</td>
<td>3</td>
<td>6.5</td>
<td>170/100</td>
<td>4.5</td>
<td>2.8</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>52</td>
<td>M</td>
<td>+</td>
<td>14</td>
<td>4.1</td>
<td>170/100</td>
<td>15</td>
<td>1.2</td>
<td>14</td>
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</table>

HT = arterial hypertension; NS = nephrotic syndrome; BP = blood pressure; sCr = serum creatinine.

*Time (days) elapsed between onset of clinical symptoms of nephrotic syndrome and start of dialysis.
administered, but was completely ineffective on urine output in 3 patients (n. 2, 4, 5) or resulted in a minimal increase of diuresis in 1 patient (n. 3). Therefore, these 5 patients had to be treated by hemodialysis 3-14 days after the onset of symptoms to control fluid overload and uremic symptoms. One patient (n. 1) had moderately reduced renal function at onset and initially responded to furosemide and spironolactone with substantial weight loss and edema reduction, but subsequently became oliguric again and insensitive to diuretics. Renal function declined and dialysis treatment had to be started 40 days after presentation. All patients underwent renal biopsy a few days after admission. No complications were recorded.

Renal biopsy findings

Light microscopy and immunofluorescence findings were consistent with MC disease and with FSGS in 4 and 2 patients, respectively (Tab. II). Of the 2 biopsies with FSGS one showed a typical “tip lesion” (Fig. 1A) in 1/12 glomeruli, while the second showed segmental occlusion of the glomerular tuft in 2/20 glomeruli. Extracapillary crescents were absent in all specimens. Prominent tubular lesions were seen in all but 1 patient (n. 1). Proximal tubules showed various degrees of acute damage such as loss of brush border, flattening of epithelial cells, and detachment of cells from the basal membrane (Fig. 1). Some mitotic
figures were observed. Proteinaceous casts were seen in some tubular lumens, some of which contained cell debris. A large amount of protein droplets was seen in many proximal epithelial cells. Interstitial oedema was minimal or absent. Scanty interstitial infiltration by mononuclear cells was seen in 3 cases. Arterial and arteriolar changes were consistent with the age of patients. The 4 specimens investigated by electron microscopy showed extensive foot process effacement of glomerular podocytes with no relevant findings otherwise.

### TABLE II
RENAL BIOPSY FINDINGS

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Glomerular pattern</th>
<th>Tubular lesions</th>
<th>Casts</th>
<th>Interstitial lesions</th>
<th>Arteriolar sclerosis</th>
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<tbody>
<tr>
<td>1</td>
<td>FSGS-TIP</td>
<td>±</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>MC</td>
<td>++</td>
<td>+ (H,N)</td>
<td>+ (I)</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>FSGS</td>
<td>++</td>
<td>+ (H)</td>
<td>+ (I,F)</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>MC</td>
<td>++</td>
<td>+ (H)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>MC</td>
<td>++</td>
<td>++(H,N)</td>
<td>+ (F)</td>
<td>++</td>
</tr>
<tr>
<td>6</td>
<td>MC</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

FSGS = focal segmental glomerulosclerosis; TIP = tip lesion variant of FSGS; MC = minimal change; N = necrotic cast (cell debris); H = hyaline casts; I = mononuclear cell interstitial infiltration; F = fibrosis.

### TABLE III
THERAPY AND OUTCOME

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Steroid therapy</th>
<th>Short-term outcome</th>
<th>Follow-up (months)</th>
<th>Relapse (n. relapses)</th>
<th>Treatment of relapses</th>
<th>Long-term outcome (sCr at last follow-up)</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>P 1 mg/kg</td>
<td>PR</td>
<td>30</td>
<td>Yes (1)</td>
<td>MP + 0.5 mg/kg (6wks), then oral CP, then cyclosporine</td>
<td>Progression to ESRD (sCr 4.5 mg/dL)</td>
</tr>
<tr>
<td>2</td>
<td>MP 3 g + P 0.5 mg/kg</td>
<td>CR</td>
<td>32</td>
<td>Yes (1)</td>
<td>MP + 0.5 mg/kg (8wks) then oral CP (8ws)</td>
<td>CR (sCr 1 mg/dL)</td>
</tr>
<tr>
<td>3</td>
<td>MP 3 g + P 0.5 mg/k</td>
<td>CR</td>
<td>60</td>
<td>Yes (2)</td>
<td>P 1 mg/kg (6 wks) then tapering doses</td>
<td>CR (sCr 0.8 mg/dL)</td>
</tr>
<tr>
<td>4</td>
<td>P 1 mg/kg</td>
<td>CR</td>
<td>60</td>
<td>Yes (3)</td>
<td>P 1 mg/kg (4 wks), then tapering doses, then oral CP (8 wks)</td>
<td>CR (sCr 0.8 mg/kg)</td>
</tr>
<tr>
<td>5</td>
<td>P 1 mg/kg</td>
<td>CR</td>
<td>24</td>
<td>No</td>
<td>-</td>
<td>CR (sCr 1.1 mg/dL)</td>
</tr>
<tr>
<td>6</td>
<td>P 1 mg/kg</td>
<td>CR</td>
<td>52</td>
<td>Yes (3)</td>
<td>P 1 mg/kg, then oral CP (8 wks)</td>
<td>CR (sCr 1.2 mg/dL)</td>
</tr>
</tbody>
</table>

CR = complete remission; PR = partial remission; P = prednisone; MP = methylprednisolone pulses; CP = cyclophosphamide; sCr = serum creatinine.
Follow-up and treatment

The duration of dialysis treatment of the 6 patients varied from 1 to 6 weeks. All patients were treated with steroids (Tab. III) early after presentation and during the dialysis treatment period. A significant reduction in proteinuria was observed in all patients at the time of renal function recovery. After a period of time from 4 to 8 weeks all patients achieved a complete or partial remission. A relapse of NS was observed in 5/6 patients when steroids were stopped or tapered. Steroids were then resumed and all but 1 patient responded. Two patients (n. 4 and n. 6) were frequent relapers and were successfully treated with oral cyclophosphamide 2 mg/kg for 8 weeks. In the patient who did not respond (n. 1), steroid treatment of the relapse had been delayed due to the occurrence of herpes zoster infection. He was treated 3 months after the appearance of the symptoms of the relapse, with 3 methylprednisolone pulses of 1 g each, followed by oral prednisone 0.5 mg/day for 4 months; he was then treated with oral cyclophosphamide for 4 weeks without benefit. Subsequently, he was treated with cyclosporine, but nephrotic range proteinuria persisted. During cyclosporine treatment the patient developed thrombocytopenia, hemolytic anemia, arterial hypertension and worsening of renal function. An hemolytic uremic syndrome related to cyclosporine was suspected and cyclosporine was stopped. The patient was treated with plasma exchange and with a new course of 3 methylprednisolone pulses. Thrombocytopenia and hemolytic anemia disappeared and renal function improved, but NS persisted. A second renal biopsy showed features of FSGS extended to the majority of glomeruli, associated with large areas of interstitial fibrosis and arteriolar sclerosis. In the following months, renal function declined progressively. An arteriovenous fistula was created and regular dialysis was started. The remaining 5 patients at the last follow-up control were in remission from NS with normal renal function.

Discussion

In the existing literature, approximately one third of children (7) and adult patients (4, 8, 9) with MC NS show a relevant reduction in renal function during the acute phase of the disease. In general, the dysfunction is completely reversible when patients go into remission. In a minority of patients, especially in adults, GFR is severely reduced and oliguria resistant to diuretic treatment develops so that renal replacement therapy becomes necessary, as it was in our cases which were selected on the basis of the criterion that they required dialysis treatment. In our study, we included patients who showed at renal biopsy minimal glomerular lesions or FSGS limited to few glomeruli, since the clinical features of this latter condition at onset are indistinguishable from those of MC disease, and because they have been included in other literature series devoted to ARF in NS (1). We excluded patients with ARF associated with severe structural glomerular changes such as crescentic or necrotizing lesions, membranous and membrano-proliferative lesions, as well as those with acute interstitial nephritis. Four out of the 6 patients were aged >50 and 5/6 were males. A severe reduction in renal function was already present at the onset of symptoms in 5/6 patients and dialysis had to be started within few days. This finding is challenging for the nephrologist, since the diagnosis of MC or FSGS is unexpected. Therefore, a renal biopsy has to be performed early in the course of the disease to be able to choose appropriate treatment. At renal biopsy we observed moderate to severe acute tubular lesions in all patients who were biopsied when renal function was severely reduced. The only patient who showed mild tubular lesions was biopsied before the ARF episode, when renal function was still preserved. Interstitial edema was minimal and cannot be considered a key factor in the pathogenesis of ARF as suggested by Lowenstein et al (10). Proteinaceous casts were scanty and their role in renal dysfunction by a mechanism of tubular obstruction advocated by some authors (11-13) is questionable. The main findings of tubular lesions observed in our cases are reminiscent of those described in biopsy specimens taken from patients with ARF due to renal ischemia (6) and have been reported in other series of ARF in NS (1). However, whether these lesions can be considered the hallmark of this condition cannot be firmly established. Some authors have compared renal biopsy findings of patients with MC glomerulopathy both with and without ARF (serum creatinine >2.0 mg/dL) and found that flattened epithelium of proximal tubules, loss of brush border and dilated lumens were the most distinctive lesion associated with renal failure (14). Similar lesions have also been found in our cases; however, we have no biopsy data taken from patients with idiopathic NS without ARF for comparison. On the other hand, the rarity of this complication in the more severe form would not have allowed such evaluation. The pathogenesis of this complication remains elusive. Hypovolemia spontaneous or induced by diuretics has been suggested by the early report of Chamberlain at (15); however, hypovolemic symptoms have rarely been described and diuretic use has been rarely reported as a precipitating factor for ARF (1). Our finding of arterial hypertension recorded in 5/6 patients and the occurrence of ARF even before any diuretic treatment is in contrast with the hypovol-
olemic hypothesis. However, the possible role of vasoactive factors triggered by a reduced effective blood volume, in inducing intrarenal ischemic lesions cannot be excluded. Pathophysiology of systemic hemodynamic and fluid distribution in NS is complex and not fully understood. Both the “underfill” and “overfill” hypothesis are substantiated by experimental and clinical data (16). According to the first hypothesis salt retention and edema formation are triggered by plasma volume reduction as consequence of fluid shift from the intravascular to the interstitial space caused by an abrupt decrease of oncotic pressure due to severe hypoalbuminemia. Some data such as renin-angiotensin-aldosterone system activation, which can be found in approximately 50% of nephrotic patients (17), enhanced release of vasopressin (18) norepinephrine secretion (19), reduced level of atrial natriuretic peptide (ANP) (20) observed during the acute phase of NS, are in line with the “underfill” hypothesis. In contrast, some studies have shown a suppressed renin-angiotensin-aldosterone system (21, 22) increased ANP (23), an impaired natriuretic response to albumin infusion (22, 24, 25), or to ACE inhibitors (26) or to head-out water immersion activation (27, 28) or to ANP infusion (29), findings that suggest a normal or expanded plasma volume and an intrinsic defect of renal sodium and water handling. Recent data from experimental models of NS support the hypothesis that abnormalities of sodium transport mechanisms along the distal tubule and collecting ducts could be responsible for an enhanced sodium and water reabsorption (30). These contrasting data taken together suggest that both an “underfill” and an “overfill” condition can develop in individual patients during the acute phase of NS (31) or can represent different phases of NS (32).

Whether patients with NS and ARF belong to one of the two hemodynamic conditions has not been fully investigated. Low or normal GFR can be found in nephrotic patients independently from the hemodynamic profile (16). Vande Walle et al measured GFR and renal plasma flow in 11 children with MC NS and oliguric renal failure before and after albumin infusion (33). Before albumin infusion GFR was significantly decreased, whereas renal plasma flow was normal and filtration fraction was reduced in most patients. There was a heterogeneous response to albumin infusion with a GFR increase in some patients and a decrease in others. Filtration fraction remained unchanged or decreased even further in 7 patients. The authors suggest that changes in glomerular permeability may have a major role in ARF occurring in MC NS (33). Other data support the hypothesis that GFR depression in MC NS is determined by the reduction of the hydraulic permeability of the glomerular capillary wall expressed by the ultrafiltration coefficient, which in turn is linked to the extensive foot process effacement of podocytes (34, 35). Therefore, it can be speculated that the ARF episodes observed in NS can be an amplification of this common dysfunction (1). However, the acute reduction of glomerular permeability per se does not justify the “ischemic” tubular lesions observed in these cases, since renal blood flow is preserved in most cases even in patients characterized by clinical symptoms of hypovolemia (31).

One of the most striking findings in our biopsy specimens was the abundance of protein droplets within the cells of proximal tubules, which reflects the uptake of a huge amount of filtered proteins. There is increasing evidence that in NS the abnormally filtered proteins including albumin and complement system components may exert a toxic effect on proximal tubular cells through several mechanisms such as upregulation of inflammatory, vasoactive and fibrogenic genes, activation of complement cascade, and induction of apoptosis (36). Therefore, it can be speculated that an exceptionally high protein overload on proximal tubular cells may be a key factor in inducing tubular injury and ARF in NS. In line with this hypothesis, other authors have shown that patients who develop ARF have a higher rate of urinary protein excretion than those who did not develop renal dysfunction during the acute phase of NS (4, 14). However, what makes these patients different from the great majority of the others still remains unexplained.

According to the data from the literature, ARF associated with idiopathic NS is in most cases a reversible condition (1). Despite the severity of clinical features of our patients, we can confirm this finding. All our patients had renal function recovery even after a prolonged dialysis treatment period. In all our patients functional recovery paralleled with the improvement of protein excretion induced by steroid therapy. Therefore, the occurrence of ARF in idiopathic NS does not preclude steroid sensitivity and suggests a prompt intervention with steroid treatment to reduce the exposure of tubular cells to the toxic effect of protein overload as soon as possible. In addition, the long-term follow-up of our patients shows that the clinical outcome of subjects that recover from ARF is similar to that observed in other series of adult idiopathic NS, with a relapsing course of the disease in most patients. Relapses were not accompanied with the recurrence of severe renal insufficiency and at the final observation all but one were in remission with normal renal function. The progressive course observed in a single patient can be explained by a delayed steroid treatment of the relapse and by the
occurrence of the hemolytic uremic syndrome which is an exceptional complication of cyclosporine treatment. Our study has some limitations; the first is the small number of patients. However, we selected only those with a severe form of ARF requiring dialysis, to focus on the cases in which in the context of idiopathic NS pose serious problems for the diagnosis and clinical management. The small number of patients observed confirms the rarity of this complication since we could collect only 6 cases among 5 nephrology centers during a period of 10 years. However, we were not able to provide adequate epidemiological data to establish the incidence of this event, since we could not define the referral population of the centers participating in the study.

In conclusion, our study provides further information concerning the clinical and pathological characteristics of patients who develop ARF in the context of idiopathic NS. This complication can be severe and unexpected and requires renal biopsy for prompt recognition and appropriate treatment. Patients with this complication are sensitive to steroids that should be administered as soon as possible with an adequate regime. Renal biopsy findings reveal an acute tubular injury produced by mechanisms not yet ascertained. A toxic effect on the proximal tubular cells related to the huge overload of proteins due to the loss of selectivity of the glomerular barrier can be hypothesized. Therefore, any effort aimed at correcting this defect with the appropriate measures has to be made as promptly as possible.

**ACKNOWLEDGEMENTS**

Electron microscopy investigations were performed by Professor Michael J. Mihatsch, Institute of Pathology, University of Basel CH. We thank Dr. Silvio Bertoli, Nephrology Unit, Multimedica, Milano for the follow-up information on patient n. 1.

Financial support: None.

Conflict of interest statement: None declared.

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Received: September 30, 2009
Revised: December 30, 2009
Accepted: January 11, 2010