Pathophysiology of acute renal failure in idiopathic nephrotic syndrome

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Introduction

Acute renal failure (ARF) is an occasional but alarming complication of nephrotic syndrome (NS).

Causes include rapid progression of the original glomerular disease, renal vein thrombosis and allergic interstitial nephritis (antibiotics, diuretics, NSAIDs). Sometimes, NS and ARF arise simultaneously following treatment with drugs such as with NSAIDs or, as described in recent years, foscarnet or interferon-alpha. In other circumstances, ARF complicates
pre-existing idiopathic NS in the absence of any of the above conditions, and haemodynamic derangements are suspected. In this report I will discuss the latter.

Clinical features

An excellent overview by Smith and Hayslett [1], covering the literature until 1992, describes the following features in 75 patients with NS and ARF: (i) most patients are elderly (~60 years of age) and hypertensive; (ii) postural hypotension is not recorded; (iii) proteinuria is severe and plasma albumin approximately half the normal level; (iv) two-thirds are male; (v) most patients exhibit severe oedema; (vi) the average length of time between the onset of the NS and ARF is 4 weeks; and (vii) most patients show complete recovery of renal function over an average period of 7 weeks. Earlier, we reviewed the literature and described roughly similar characteristics [2].

However, this is not the only presentation of ARF with NS. In fact, the presentation can be very different, as it can also occur early on in the disease, with a very fast occurrence and resolution. This feature is found more commonly in children and occasionally in (young) adults (see below). This form of ARF may be reported less often because it is milder in both severity and duration. Protracted ARF necessitating dialysis and followed by delayed recovery occurs rarely in children [1,2]. However, one series reported that of 27 children referred for acute dialysis treatment, six (27%) had nephrosis [3]. Recently, four more such children were reported; in three of these, the dialysis period was only a few days [4].

Early reports of ARF in adults with NS mentioned hypotension and sometimes overt hypovolemic shock preceding ARF. It was considered that NS patients were more liable to develop hypotension and subsequently ARF upon circulatory challenges such as fluid withdrawal, surgery or septicemia. However, a thorough review of reported cases could not identify such factors in many cases [1,2]. Indeed, blood pressure was mostly normal or somewhat elevated. Two clinical presentations are observed in children who develop ARF in the initial phase of NS. In one group blood pressure is low and classical hypovolemic symptoms (pallor, cold skin, tachycardia, abdominal cramps) are present. Laboratory examination may show severe haemoconcentration [5]. These symptoms, as well as oliguria, respond favourably to albumin expansion. In the other group, blood pressure is normal or high [4], and albumin infusion can be dangerous. Both types are characterized by marked proteinuria, but their plasma albumin is not necessarily low yet.

Pathology

Most patients (85%) with ARF and NS have minimal lesions [1]. In 60%, tubulointerstitial changes compatible with acute tubular necrosis (ATN) are present: rarefaction of proximal tubule cells, tubular cell necrosis, granular casts, interstitial oedema and slight peritubular infiltration with mononuclear cells. In 40% no tubular damage is found, although there is considerable interstitial oedema [1,6]. Jennette and Falk [7] compared 21 patients with minimal lesion NS and ARF (plasma creatinine > 177 µmol/l; average 486 µmol/l) with 50 patients with minimal lesion NS and normal kidney function. Histological signs of tubular necrosis were present in 71% of the ARF group, but never in the non-ARF group. The ARF group also showed more severe signs of arteriolosclerosis (intimal hyperplasia and hyalinosis), which was considered important for the pathogenesis of the ARF [1,7]. Biopsies taken from children in whom ARF necessitated dialysis showed similar changes, compatible with ATN [4]. Renal histology during early, quick resolving ARF is not available.

Pathophysiology

In view of the different clinical presentations, ARF in the NS is not a single, uniform pathophysiological entity. Factors that can be singled out to contribute to the decrease in glomerular filtration rate (GFR) are a low renal perfusion pressure, a decreased filtration coefficient, high intratubular pressure, ATN, interstitial nephritis and interstitial oedema.

In the case of overt hypotension, a pre-renal cause can be suspected. This is encountered particularly in children with persistent proteinuria that is so severe that blood volume cannot be maintained, such as in congenital NS. In children with relapsing minimal lesion NS, hypovolemic ARF may be encountered early during a relapse. The acute start of heavy proteinuria probably causes a disequilibrium between plasma and interstitial albumin concentrations. However, when plasma protein drops, proteinuria diminishes, and is often insufficient to remain a threat for hypovolemia as in congenital NS. We have tried to amend this in children presenting with early relapse of minimal lesion NS [8]. Half of them had ‘hypo-volemic symptoms’. Compared with non-symptomatic children, they had stimulated neurohumoral factors and strong tubular sodium reabsorption, and a suppressed urinary dilution capacity, compatible with the presence of a pre-renal factor. However, even in these children renal plasma flow was high, and the decreased GFR thus reflected a decreased filtration fraction.

In adults, proteinuria is generally not marked enough to endanger the circulation [9]. Relapses of minimal lesion NS develop more slowly, but may occasionally be acute, as occurs in children. It cannot be excluded, however, that adults with established NS are more liable to develop ARF if they suffer from some other complications such as septicemia or blood loss. Indeed, blood volume that is normal while recumbent may drop below normal when standing.
On the other hand, mobilization of excess tissue fluid in hypoproteineemic conditions is highly efficient [9]. Excess fluid can mostly be removed without inducing hypotension or renal failure. However, complete removal of excess fluid may create an unsteady condition were changes in blood volume cannot be compensated.

Approximately 30% of children [10] and adults [11] with idiopathic NS have a significant decrease in GFR. This is due to an intrinsic filtration impairment, since filtration fraction is low. Conceivably, ARF may reflect worsening of this intrinsic problem. However, glomerular changes, i.e. obliteration of epithelial slit pores as visible with electron microscopy, are not correlated with the reduction in GFR in humans. Filtration can also be impaired by a high intratubular pressure caused by protein casts [1,2], but this possibility has received little attention. The following case history illustrates the possible importance of this factor.

Case history

A 23-year-old male consulted us for treatment of his third relapse of minimal lesion NS. Two days earlier he had noticed renewed proteinuria (dipsticks) and had started treatment with prednisone 100 mg. On admission his blood pressure was high (150/90 mm Hg), plasma creatinine elevated (237 µmol/l), and plasma albumin only moderately decreased (31 g/l). He voided only small amounts of gel-like urine, which contained > 120 g/l albumin and virtually no sodium. Prednisone treatment was continued, proteinuria started to decline rapidly after 4 days and renal function with the appropriate sodium excretion recovered.

This case shows that early after the start of a relapse, glomerular albumin leakage can be so heavy that it is quite conceivable that tubules become obstructed, and renal failure develops while plasma albumin is not yet decreased. Hypovolemia, due to an imbalance in albumin distribution, was unlikely is this patient since the blood pressure was high. Although we have seen this feature more than once, this presentation is probably uncommon. Literature data on urinary protein content in initiating NS is scanty and absent in papers on ARF early in NS. It is our experience that this type of ARF resolves within days. Treatment with diuretics, meant to support the volume balance, may in fact work by decreasing tubular protein deposition.

This poses a dilemma in the treatment of patients with early ARF during a severe relapse of NS. It is understandable and probably wise to expand patients who show hypovolemic symptoms. However, if albumin infusion is used, this should be limited as much as possible, and used only to overcome the (usually) transient hypovolemic symptoms. Prolonged albumin infusion will only increase the risk of tubular protein clogging (by maintaining high protein filtration), hypertension and pulmonary congestion. Oliguria per se is not a good indicator of hypovolumia, since it can also be due to protein clogging. In this respect, it is illustrative that children with minimal lesion NS who are treated with hyperoncotic albumin infusion to overcome renal sodium retention often develop hypertension, distended neck veins and renal failure [12,13].

The pathogenesis of ARF in adults with established idiopathic NS is less clear. Even though the histology may suggest ATN in many instances, it remains unclear why it develops. The observed arteriolar sclerotic changes [7] suggest that these patients are particularly vulnerable to ischaemic insults. However, it remains uncertain what that insult is, in view of the normal or often high blood pressure at the time of established ARF. Of course, it cannot be excluded that a phase of lower blood pressure has preceded ARF, but this is not apparent in the majority of available reports. A factor that has not been studied systematically is the possible contribution of renal artery stenosis, which is common in elderly subjects and perhaps even more in those with NS [14], and might increase the vulnerability to variations in blood pressure. Tubular obstruction by protein casts is not a likely cause for this form of ARF. On the other hand, we have to consider that increased filtration and, subsequently, tubular reabsorption of albumin may contribute to an interstitial inflammatory response. A role of interstitial oedema leading to tubular obstruction and therefore reduced GFR has been claimed for patients in whom the kidneys showed marked oedema, and in whom renal failure disappeared with volume withdrawal induced by dialysis or diuretic treatment [6]. In some instances, however, the recovery of GFR occurred very late, and prednisone and oedema treatment were often introduced together, so that a clear-cut relationship with volume withdrawal could not be established.

Summary

ARF can occur early during a rapidly developing relapse of NS, due to either a temporary blood volume imbalance or (probably) to an initially heavy glomerular protein filtration, clogging the tubules. This form of ARF is seen mainly in children and resolves quickly. Albumin infusion may be helpful in the former type of ARF, whereas it may induce or aggravate the latter. A protracted form of ARF, necessitating dialysis, may occasionally develop in adults. Pathology shows changes compatible with ATN and/or severe interstitial oedema. This form of ARF is preponderant in the elderly, and increased sensitivity to ischaemia due to pre-existent arteriolar sclerosis is suspected. Renal function usually recovers, but this may take weeks or even months. Specific treatment (steroids) and oedema removal have been claimed to play a role in this recovery, but this is unproven since, understandably, such treatment is never omitted.
References