Liver disease and renal dysfunction

Aisling O'Riordan

Abstract

Renal dysfunction is a relatively frequent complication of liver disease. Acute kidney injury and chronic kidney disease can co-exist with acute or chronic liver disease, or occur sequentially. These patients have increased morbidity and reduced survival and so there is renewed emphasis on improving definitions of renal dysfunction in this patient population to facilitate early recognition and prompt treatment. This article outlines a practical approach to investigation and management of these complex and challenging patients.

Keywords acute kidney injury; acute liver failure; chronic kidney disease; cirrhosis; hepatorenal syndrome

Introduction

Both acute kidney injury (AKI) and chronic kidney disease (CKD) often complicate liver disease, and renal dysfunction can be both a diagnostic and therapeutic challenge in this patient population. There is a variety of potential causes including a common underlying systemic disease such as hepatitis B or C. More commonly however, renal dysfunction occurs as a consequence of a primary liver disorder, as in hepatorenal syndrome (HRS).[1]

Even small increments in serum creatinine are linked with increased mortality.[2] Hence, outcomes for patients with liver disease complicated by renal failure are often particularly poor.[3,4] This is highlighted by the fact that serum creatinine is one of the components of the Model for End Stage Liver Disease (MELD) score used to prioritize patients with severe liver disease for liver transplantation.

Early recognition and identification of the cause of the renal dysfunction with a view to initiating prompt treatment is crucial. As a result, there has been an increased focus on refining definitions of renal dysfunction in liver patients, improving our understanding of the pathogenesis, identification of better biomarkers and development of novel therapeutic interventions.[5,6]

Incidence

AKI is a common complication of acute or fulminant liver failure (ALF). In one study evaluating renal function in an intensive care unit population with ALF following paracetamol overdose, 65% of patients developed AKI stage 3 during follow-up. The 'RIFLE criteria' were used to define AKI in that instance.[7] Paracetamol is an independent risk factor for developing AKI in those with ALF, and AKI is less common in those with an alternative underlying aetiology.[8]

Aisling O'Riordan *MB BCh BAO MRCPI MD is a Consultant Nephrologist at the Renal Department, Royal Free Hospital, Royal Free NHS Foundation Trust, London, UK. Competing interests: none declared.*

In those with cirrhotic chronic liver disease, the incidence of renal complications also depends on the underlying cause. This was well illustrated in a study evaluating the aetiology of renal failure (defined as a serum creatinine concentration greater than 133 micromol/litre in two consecutive measurements performed within a 48-hour period) in over 460 hospitalized cirrhotic patients. The investigators found that most experienced renal failure in the context of acute illness such as infection (46%), hypovolaemia (32%), HRS (13%) or nephropathy due to a parenchymal cause (9%).[9]

HRS is a distinct type of renal failure in this patient population in that it is functional in nature and potentially reversible once the underlying portal hypertension is treated. The incidence of HRS in patients with cirrhosis and ascites is reported to be between 18% within 1 year of diagnosis and up to 40% at 5 years.[10]

AKI is also a relatively frequent complication of liver transplantation, occurring in up to 61%. It has also been shown that up to 18% go on to develop CKD stage 4–5 by 5 years post-transplantation, partly due to the nephrotoxicity of calcineurin-inhibitor immunosuppression.[7,11]

Finally, an underlying diagnosis of CKD occurs in approximately 1% of all patients with cirrhosis.[5]

Definition

Definitions for AKI and CKD have evolved in recent years and consensus classifications are now used widely. Hepatorenal syndrome is a unique functional form of renal impairment seen in patients with portal hypertension and this has its own specific definition (Table 1).[5]

Not all patients with renal dysfunction in the context of liver disease have HRS or meet these diagnostic criteria. Serum creatinine is not a very good marker of renal function in this group and early diagnosis of evolving renal impairment can be missed. This has led to delay in the recognition of AKI and CKD in cirrhotic individuals. In 2011, a working party comprising members of the International Ascites Club and Acute Dialysis Quality Initiative proposed new definitions for renal dysfunction in patients with cirrhosis.[5] These are outlined in Table 2. This group also proposed the term 'hepatorenal disorders' to encompass all forms of renal dysfunction in those with liver disease, including AKI, CKD and HRS.[10]

Causes and pathogenesis

The pathogenesis of hepatorenal disorders in the context of liver disease is complex and depends on the trajectory of the decline in renal function and whether the patient has underlying ALF or cirrhotic chronic liver disease.[1,4,12] To highlight this, a list of some of the possible causes of renal failure in the context of liver disease is outlined below in Table 3.

The pathogenesis of AKI complicating ALF is not fully understood. Renal acute tubular necrosis or interstitial nephritis can develop as a consequence of renal hypoperfusion, leptospirosis, salicylate, mushroom or paracetamol poisoning. It should also be noted that any pre-renal cause of AKI in this patient group could cause ischaemic tubular injury if the insult is prolonged and untreated. In other patients with ALF, the physiology resembles that in patients with cirrhosis and HRS, with intravascular volume depletion and low systemic vascular resistance.[13] A study

Definition of hepatorenal syndrome

A serum creatinine over 133 micromol/litre in a patient:

- with cirrhosis and ascites
- in whom there is no shock, recent use of nephrotoxins or improvement in renal function after at least 2 days of diuretic withdrawal and fluid resuscitation with albumin (1 g/kg of weight per day up to a maximum of 100 g/day)

There also needs to be:

- no evidence of parenchymal renal disease (i.e. proteinuria of over 500 mg/day, haematuria or abnormal renal radiological imaging)

Table 1

evaluating 308 patients admitted to an intensive care unit with ALF showed that 67% developed varying degrees of renal dysfunction; factors that independently associated with AKI included age, fulfilling the King's College Hospital prognostic criteria, hypotension, paracetamol-induced ALF, infection and the systemic inflammatory response syndrome.[8]

The pathogenesis of HRS is unique.[6,14] There is no intrinsic renal injury; the problem is physiological or functional in nature. It occurs classically in patients with cirrhotic liver disease and portal hypertension, in whom release of vasoactive factors such as nitric oxide cause splanchnic arterial vasodilation and reduced systemic vascular resistance, resulting in a lower mean arterial pressure. To compensate and maintain arterial blood pressure, cardiac output increases and a hyperdynamic circulation ensues. However, as cirrhosis progresses, cirrhotic cardiomyopathy may become more clinically apparent. This has become a recognized entity in the last decade and is defined by the presence of systolic and diastolic dysfunction, particularly under stress. In order to maintain mean arterial blood pressure, the sympathetic nervous and renin–angiotensin systems become activated, and increased secretion of anti-diuretic hormone may also occur. This triggers vasoconstriction in renal vessels and overcomes the release of local vasodilators, such as prostaglandins, and the kidney's ability to auto-regulate its own blood supply. The consequence is renal hypoperfusion, a form of pre-renal failure. Increased aldosterone production causes excessive salt and water retention resulting in ascites, one of the key clinical manifestations of HRS.

Hepatorenal disorders

Acute kidney injury (AKI)

An increment in serum creatinine by 50% from the previous baseline (if known) or a rise in creatinine by 26 micromol/litre in under 48 hours. Hepatorenal syndrome (HRS) type 1 is one cause.

Chronic kidney disease (CKD)

A glomerular filtration rate (GFR) of under 60 ml/minute for over 3 months as calculated using the Modification of Diet in Renal Disease 6 variable equation. HRS type 2 is one cause.

Acute-on-chronic kidney disease

AKI (as defined) in a patient with cirrhosis who also has CKD as described above.

Table 2

If the ascites is tense this may increase intra-abdominal pressure, further compromising renal perfusion.

Finally, it is important to point out that many patients with acute or cirrhotic liver disease will also have pre-existing CKD. In the USA, the prevalence of chronic liver disease has increased over the past 10 years. In the western world, hepatitis B and C, alcoholic liver disease and haemochromatosis are the most common causes of liver disease. Non-alcoholic fatty liver disease is also increasing in prevalence. Many of these patients will be obese and have diabetes mellitus, so underlying focal segmental glomeruloscerosis and or diabetic nephropathy are also possible.[15]

Clinical presentation

The clinical presentation varies.[1,6,16] A careful history and examination will often provide the diagnosis or a differential leading to appropriate investigations.

History

Common symptoms of chronic liver disease include jaundice, ascites, pruritus, nausea, reduced appetite and lethargy, many of which can also occur with uraemia. There may be features of sepsis or abdominal pain in those with peritonitis or a history of melaena or haematemesis. Patients may be confused, disorientated and have a reduced level of consciousness or a history of seizures, suggesting a developing encephalopathy. These patients will often have a longstanding diagnosis of cirrhosis.

Conversely, patients can present acutely and gravely unwell with ALF. If the precipitating event is not clear it is important to take a history of recent medication use including over-the-counter and herbal therapies. A sexual, illicit substance and alcohol history should also be obtained along with information about recent foreign travel, viral illnesses, hobbies and occupation. If the patient is incapable of giving a history, input from family or acquaintances is crucial.

Examination

Stigmata of chronic liver disease may be apparent such as clubbing, palmar erythema, asterixis, spider naevi, muscle wasting and gynaecomastia. In those with portal hypertension, ascites or splenomegaly will often be present. The liver may or may not be enlarged and tender.

A careful assessment of volume status should be performed, to document dehydration, or fluid overload with pulmonary and peripheral oedema. If the patient is still passing urine, hourly urine output should be recorded, if necessary by catheterizing the patient.

A urine dipstick is essential in helping to differentiate pre-renal from intrinsic renal disease and HRS. A rectal examination should also be performed looking for melaena.

Investigations

Measuring renal function

Because of the high prevalence of renal dysfunction in patients with liver disease renal function must be monitored regularly. If renal impairment is identified it is important to record the rate of decline, to distinguish acute and chronic causes. However, assessment of renal function using serum creatinine or estimated