Glomerular IgA deposition in liver disease

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Introduction

IgA nephropathy associated with liver disease (hepatic IgAN) is the commonest form of secondary IgAN. It is particularly common in alcoholic liver disease, which itself is associated with disorders of the IgA immune system [1,2] but also occurs in other forms of cirrhosis and chronic hepatitis. It is characterized by microscopic haematuria, proteinuria, elevated serum IgA levels and mesangial deposits of IgA. Although usually a clinically silent condition, a small percentage of patients present with nephrotic syndrome and renal impairment that can rarely progress to end-stage renal failure.

Is hepatic IgAN a distinct clinicopathological entity?

An association between glomerular disease and cirrhosis has been known since the 1950s although early autopsy studies did not always take account of viral infection, bacterial sepsis, and other factors that might also provoke glomerular injury. Glomerular lesions are reported in more than 50% of cirrhotics [3] and this rises to 100% in studies of end-stage liver disease [4]. Although minor glomerular damage and mesangial proliferation are commonest, a range of other light microscopic changes have been described in cirrhosis including mesangiocapillary glomerulonephritis (GN), membranous nephropathy, and crescentic GN. Studies from the 1970s onwards when immunofluorescence (IF) came into use confirmed that mesangial IgA deposition was the commonest pattern seen present in 50–90% of cirrhotics with GN [3]. Although the majority of these reports are in patients with alcoholic liver disease, glomerular disease with mesangial IgA is also described in patients with other chronic liver disease and therefore, although this is sometimes described as cirrhotic GN, the term hepatic IgAN is preferred. The three most commonly found patterns of glomerular disease in cirrhotics are hepatic IgAN, HCV-associated GN, and hepatic glomerulosclerosis, i.e. an MCGN-

Renal histology

The light microscopic features of hepatic IgAN are similar to primary IgAN. There is variable widening of mesangial matrix, thickening of the capillary wall, mesangial hypercellularity, usually diffuse and sometimes segmental, with mesangial electron-dense deposits. Occasionally a mesangiocapillary pattern is seen and rapidly progressive crescentic GN has also been described. Mesangial IgA predominates but is often associated with lesser amounts of IgG, IgM, or C3. As in primary IgAN, mesangial IgA may be seen in the absence of light microscopic changes. Ultrastructural features may, however, be distinctive: mesangial interposition and splitting of the GBM are more commonly seen than in primary IgAN.

Clinical features of hepatic IgAN

Autopsy studies indicate that hepatic IgAN, like primary IgAN, may be clinically silent and is usually an asymptomatic condition: the majority presenting with microscopic haematuria, proteinuria, and in some cases mild renal impairment [6]. As in primary IgAN microscopic haematuria is the dominant urine abnormality. Less commonly patients can present with nephrotic
syndrome (although this may not be easy to assess in the presence of hypoalbuminaemia due to liver disease) and renal failure. One consecutive study in cirrhotics indicated that 9.6% of cirrhotics have a nephritic urine and 1.6% are nephrotic [7]. The activity of the urinary sediment correlates with the severity of the glomerular lesions and degree of mesangial cell proliferation [8]. The disease is often static and only rarely does it progress to end-stage renal failure. No correlation has been found between the severity of liver failure and the extent of the glomerular disease. There is no established treatment for hepatic IgAN and the prognosis depends on the progression of the hepatic disease. There is no consistent evidence that improvement in the hepatic disease improves the renal disease, although a case has been reported in which surgical correction of portal hypertension in a child was associated with remission of nephrotic syndrome due to hepatic IgAN [9]. Limited re-biopsy data suggest that the glomerular disease usually remain morphologically stable over a number of years.

The human IgA system

IgA synthesis

In man 90% of serum IgA is monomeric IgA1 and marrow derived. The majority of IgA synthesis in the body, however, is mucosal, predominantly polymeric IgA (pIgA) with IgA1 and IgA2 in about equal proportions. This pIgA reaches mucosal fluids by translocation through the epithelium via the polymeric immunoglobulin receptor, during which process the pIgA gains secretory component (SC) and becomes secretory IgA (sIgA). In health there is little or no communication between the mucosal and systemic immune systems, and little mucosal pIgA and virtually no sIgA reach the circulation.

IgA clearance

The human liver has two routes for IgA metabolism. Hepatocytes express an asialoglycoprotein receptor which binds IgA1 via asialylated O-linked terminal glycans; the receptor–IgA complex then being endocytosed and presented to the lysosomal apparatus for degradation. In addition, Kupffer cells express an Fc receptor for IgA (FcγR). FcγR are also expressed on circulating monocytes where they represent a further route of IgA clearance.

Animal models of hepatic IgAN

There are significant differences between the IgA immune system in man compared to laboratory animals. This includes differences in the structure of IgA subclasses, particularly IgA1 and in hepatic clearance of IgA. This restricts the direct application to human disease of rodent models of mesangial IgA deposition provoked by liver injury, such as administration of carbon tetrachloride or alcohol, and bile duct ligation. Consequently in hepatic IgAN, just as in primary IgAN, lessons about the prime mechanism of mesangial IgA deposition cannot easily be learnt from animal models and must largely be inferred from human studies.

IgA system abnormalities in hepatic IgAN

Serology

Raised serum IgA levels (up to 2–4 times normal) are strongly correlated with both alcoholic liver disease and the presence of IgA mesangial deposits [8,10,11]. Increased circulating IgA antibodies against common food and microbial antigens are reported in chronic liver disease. Circulating IgA immune complexes (IgAIC) are elevated in up to 80% of patients with alcoholic cirrhosis, and are higher in the presence of glomerulonephritis [12,13]. A major proportion of these complexes may be cryoglobulins (present in up to 40% of cirrhotics). There is no correlation between the IgAIC levels and degree of liver damage. Both IgA1 and IgA2 levels are found to be elevated and the IgA2 levels are proportionally higher in most studies [14]. The ratio of IgA1:IgA2 is not linked to degree of liver damage [15]. Whereas in health 90% of circulating IgA is monomeric, pIgA represents 25–45% of serum IgA in alcoholic cirrhosis [11]. Serum sIgA also starts to increase as liver damage becomes apparent [14] possibly through interruption of normal transepithelial mucosal transport of pIgA due to the adverse effects of alcohol or other toxins. C3 complement levels are often depressed but it is not clear to what extent this represents consumption by IC or cryoglobulins, or reflects failing liver synthesis.

Tissue IgA deposition

pIgA1 is the predominant form of IgA in mesangial deposits in primary IgAN, and the majority of evidence favours the same pattern in hepatic IgAN despite the increase in circulating IgA2. Studies of IgA sub-class distribution in hepatic IgAN have been contradictory, probably due to problems with reagent specificity. One early study suggested that IgA2 was frequent in mesangial IgA deposits, but this study also overestimated IgA2 in primary IgAN [16], suggesting that a later study reporting dominance of IgA1 in hepatic IgAN may be more reliable [17]. In hepatic IgAN there is also SC binding of mesangial IgA1, indicating the presence of pIgA [12], although SC itself is not present so that sIgA is not being deposited in the mesangium. Hepatic IgA deposits are a particular feature of alcoholic liver disease seen in 78% of alcoholics as opposed to only 12% of non-alcoholic liver disease, IgA1 being found in a continuous pattern along the hepatic sinusoids [15].
What is the pathogenesis of hepatic IgAN?

Although hepatic IgAN shares many features with primary IgAN, particularly mesangial deposition of pIgA1 and a similar range of glomerular injury, it cannot be assumed that there is a common pathogenesis. Abnormalities of liver clearance of IgA and of the cellular control of IgA production described in liver disease may influence the distribution and behaviour of IgA, leading to a common pattern of disease by differing mechanisms.

Increased pIgA production

Increased circulating IgA and IgAIC may represent the exaggerated response of a normal IgA immune system to excess antigen exposure, resulting from diminished mucosal integrity perhaps due to a direct toxic effect of alcohol.

However, there is some evidence for intrinsic IgA system hyperactivity. In alcoholic cirrhosis peripheral blood B cells have increased spontaneous and PHA-stimulated production of IgA in vitro and there is some evidence this is driven by abnormal T cell cytokine patterns [18]. Peripheral blood mononuclear cells also have an enhanced IL-6 response, which in turn causes further IgA secretion by B cells and thus may promote an auto-amplification loop in vivo [19]. It is difficult to define a marrow or mucosal system abnormality on the basis of such data since the destination of the circulating trafficking B cells used in these studies cannot be determined.

Production of abnormal IgA

In primary IgAN, circulating IgA1 has been shown to have abnormal O-glycosylation at the hinge region, which may modify its molecular interactions, influencing mesangial deposition and subsequent glomerular injury through interactions with matrix proteins, IgA receptors on mesangial cells and white cells, and complement [20,21]. It may also affect its interactions with receptors involved in its clearance. IgA glycosylation has not yet been studied in hepatic IgAN.

Origin of the deposited IgA?

In primary IgAN there is now strong evidence that abnormal pIgA production occurs in the marrow rather than the mucosa. This question has not yet been addressed in hepatic IgAN. There appears to be some mucosal spillage of sIgA into the circulation in cirrhosis, but since sIgA is not reported in mesangial deposits this may not be directly relevant to the pathogenesis.

Decreased IgA clearance

The fractional catabolism of pIgA is reduced in alcoholic cirrhosis [14] and there is also evidence that all hepatic removal routes for IgAIC are impaired [22]. Impaired clearance of IgA may result from alterations in the structure of either the receptor, the IgA molecule or surface distribution of the receptor. In health the ASGPR is restricted to the sinusoidal and lateral surfaces of hepatocytes, but in cirrhosis the ASGPR is located predominantly on the canalicular surface [23] perhaps reflecting a loss of hepatocyte polarity.

There is also evidence that in alcoholic liver disease the expression of Fcγ receptors is reduced on circulating monocytes and that endocytosis of IgAIC is defective [24], which may also contribute to reduced IgA clearance.

Why does IgA deposit in the mesangium?

There have been no direct studies of the mechanism of mesangial IgA deposition in hepatic IgAN. The presumption that the mesangial deposits represent IgAIC has not been directly confirmed, and there are no studies reliably identifying antigens within the mesangial deposits. Any possible genetic basis for susceptibility to hepatic IgAN or its progression has not been explored. The explanations for variable glomerular injury in hepatic IgAN are no clearer than in primary IgAN.

Conclusion

IgAN is a relatively common complication of chronic liver disease, particularly alcoholic cirrhosis, although only in a minority will it have a substantial clinical impact. There is no specific treatment for those who develop nephrotic syndrome and renal impairment. Apart from meeting the therapeutic needs of this small group of patients, further studies of the pathogenesis of hepatic IgAN may provide valuable new insights into IgA pathobiology, and may also expand our understanding of the range of mechanisms of tissue IgA deposition, which may provide new insights into primary IgAN.

References


