Nephropathy associated with heroin abuse in Caucasian patients

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Abstract

Background. Renal disease is a complication of heroin addiction. Using renal biopsies in Caucasian patients, we studied the types of nephropathy associated with heroin abuse.

Methods. Nineteen renal biopsies were performed on heroin addicts between January 1993 and December 2001. The indications for renal biopsy included proteinuria with or without renal insufficiency.

Results. All 19 patients had serological evidence of hepatitis C virus (HCV) infection, one had hepatitis B virus surface antigen and three were HIV positive. Thirteen patients (68.4%) were found to have membranoproliferative glomerulonephritis (MPGN), 12 with type I and one with type III. Of the remaining patients, two had chronic interstitial nephritis, two had acute proliferative glomerulonephritis, one had amyloidosis and one had granulomatous glomerulonephritis with interstitial nephritis. No apparent decline in the incidence of renal disease was observed.

Conclusions. In this cohort of male Caucasian heroin addicts, HCV-associated MPGN was the most frequent pattern of nephropathy, showing that the nephropathy associated with heroin abuse in Caucasians is not of the focal and segmental glomerulosclerosis type, in contrast to previous reports on African-Americans. This aspect may have important implications for patient management and prognosis.

Keywords: hepatitis C; heroin; membranoproliferative glomerulonephritis; nephropathy

Introduction

Massive proteinuria as a complication of heroin addiction has been recognized since the 1970s [1–3]. Progressive glomerulopathy leading to nephrotic syndrome and renal insufficiency in heroin addicts was first described by Rao et al. [1] and was named ‘heroin-associated nephropathy’ (HAN). Renal biopsy data in HAN patients have consistently disclosed focal–segmental glomerulosclerosis (FSGS) with deposition of IgM and C3 in areas of sclerosis [1,2,4]. Similar kidney lesions have been seen in intravenous users of pentazocine and tripelennamine [5].

The descriptions of HAN have been almost exclusively among black patients [1,4,6,7], although there have been reports of cases among Caucasians [6]. About 90% of HAN patients were male and usually between 18 and 45 years of age [1,6,7]. The duration of their drug abuse varied from 6 months to 30 years before the onset of renal disease [1,2,7]. Most patients presented with nephrotic syndrome [1,2,7]. HAN was unresponsive to immunosuppressive therapy, and progression to end-stage renal disease (ESRD) commonly occurred in a period of months to 2–3 years after the detection of proteinuria [1,2].

The pathogenesis of HAN was unknown. Likely causes were bacterial or viral contaminants, toxins in substances used to dilute the heroin, or heroin itself [3,7]. It has been suggested that black people might have a genetic predisposition for developing HAN [6–8].

In the 1980s, the incidence of HAN peaked [6], and FSGS associated with intravenous heroin abuse was described as a major cause of nephrotic syndrome and ESRD in addicts. HAN was considered a widespread problem in the United States, and the cost of treating patients with HAN and ESRD was substantial [6].

In 1984, a decade after the description of HAN, Rao et al. [9] described a new entity recognized, again, in heroin addicts and also in homosexual men, namely a rapidly progressive renal disease in association with the acquired immunodeficiency syndrome, termed ‘HIV-associated nephropathy’ (HIVAN). Its characteristic pathological pattern was FSGS, and >85% of cases of HIVAN occurred in black (African-American) patients [10]. The disease usually resulted in nephrotic-range proteinuria (NRP) and unrelenting progression to ESRD, often within months of presentation.
Interestingly, the appearance of HIVAN was accompanied by a sharp decrease in the incidence of new cases of HAN since 1989. In 1995, Friedman and Rao [11] reported a decline in the incidence and then an absence of new cases of HAN-associated ESRD since 1990, although no decline was seen in heroin addiction.

At our institution, we observed the continued appearance of new cases of renal disease in Caucasian intravenous drug addicts, characterized by heavy proteinuria and renal failure. That prompted us to review the clinical and pathological data from all parenteral heroin addicts who were seen in our department and who had renal biopsies performed because of significant kidney disease between 1993 and 2001.

Subjects and methods

A total of 19 renal biopsies were performed in Caucasian males with a history of intravenous heroin abuse who were admitted to the Department of Nephrology at our hospital between January 1993 and December 2001. These 19 biopsies represented 1.8% of the 1058 native kidney biopsies performed in the period under study.

All patients had been referred for evaluation of significant proteinuria of unknown aetiology, with or without azotaemia. The patients’ charts were reviewed for age, sex, race and presenting clinical and laboratory features at the time of the renal biopsy. The following definitions were used: hypertension, a systolic pressure of >140 mmHg or a diastolic pressure of >90 mmHg or both; NRP, a 24 h urine protein excretion of ≥3.5 g; haematuria, the presence of >5 red blood cells per high power field on microscopic examination of the urinary sediment; hypoalbuminaemia, a serum albumin level of ≤3.5 g/dl; nephrotic syndrome, the combination of NRP, hypoalbuminaemia and oedema; and renal insufficiency, a serum creatinine level of >106 μmol/l (1.2 mg/dl).

Renal biopsies were performed percutaneously, the majority under ultrasound guidance. Kidney tissue was appropriately fixed and examined by light, immunofluorescence and electron microscopy according to standard techniques. Serial sections, 3 μm thick, were stained with haematoxylin and eosin, periodic acid-Schiff and silver methenamine or trichrome-Masson stains. Routine immunofluorescence microscopy was performed on 5 μm cryostat sections using polyclonal FITC-conjugated antibodies to IgG, IgM, IgA, C3, C1q and fibrinogen. In 18 of the 19 patients, adequate glomerular tissue was available for electron microscopy.

For each biopsy specimen, the severity of the lesions observed by light microscopy (glomerular proliferation, glomerular sclerosis, tubular atrophy and interstitial infiltration) and the intensity and extent of the immunofluorescence microscopy findings were graded semi-quantitatively on the following scale: 0, absent; 1+, slight; 2+, moderate; and 3+, marked.

Serological data for HIV, hepatitis B virus (HBV) and hepatitis C virus (HCV) for the study cohort were obtained. Chronic HCV infection was diagnosed by the presence of serum antibodies against HCV proteins. Serum samples were tested for evidence of HBV infection by measuring hepatitis B surface antigen, anti-hepatitis B core antigen IgG and anti-hepatitis B surface antigen, and HIV infection was diagnosed by the presence of serum antibodies against HIV (types 1 and 2).

Data are presented as arithmetic means ± SD.

Results

The incidence of renal biopsies performed on patients with a history of heroin abuse was determined for the period between January 1993 and December 2001 (Figure 1). There was no decrease in the incidence of renal biopsies in heroin addicts during the 9 years evaluated. Of the 19 patients, six were diagnosed from January 1993 to December 1995, five from January 1996 to December 1998 and eight from January 1999 to December 2001.

Clinical features

The demographic profiles, clinical presentations and laboratory findings at the time of renal biopsy are

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Fig. 1. The rate of renal biopsies in patients with a history of heroin abuse is plotted as a percentage of total native renal biopsies performed between January 1993 and December 2001.
summarized in Table 1. All patients were Caucasian males with a mean age of 31 ± 4.9 years. The duration of intravenous heroin abuse ranged from 2 to 20 years prior to the documentation of their renal disease, though in four patients the duration could not be ascertained. Six of the patients also had a history of cocaine use.

The reasons for performing renal biopsies were nephrotic syndrome in 15 patients and non-nephrotic proteinuria in the remaining four. The mean level of proteinuria was 4.5 ± 1.8 g/l. A slight reduction (at least) in renal function was observed in most patients. Plasma creatinine levels >106 μmol/l (1.2 mg/dl) were present in 13 patients (68.4%). Mean plasma creatinine levels were 169.8 ± 114.3 μmol/l (1.9 ± 1.3 mg/dl). Eighteen patients had microscopic haematuria and 14 had hypertension. Other clinical data included mildly elevated serum aminotransferase concentrations in nine patients (47.3%) and hypocomplementaemia in 13 (68.4%).

All patients had serological evidence for HCV infection (confirmation by PCR was obtained in only four patients), one had HBV surface antigen and three were HIV positive (Table 2).

Pathological features

The results of the light, immunofluorescence and electron microscopy of the 19 kidney specimens obtained from these patients are summarized in Table 3. The mean number of glomeruli observed in each biopsy was 12.6 ± 6.5.

Of the 19 patients, 13 (68.4%) were found to have membranoproliferative glomerulonephritis (MPGN), 12 with type I and one with type III (Figure 2). Under light microscopy, the most common histological features observed in patients with MPGN were thickened glomerular capillary walls and marked endocapillary hypercellularity, frequently with a lobular pattern. In four patients, crescents were present (involving 6, 25, 32 and 50% of the glomeruli, respectively). Immunofluorescence microscopy showed granular deposits of immunoglobulins, mainly IgM and C3. Ultrastructural microscopy showed mesangial interposition and characteristic subendothelial immune-complex type deposits in the 12 patients with type I MPGN. Occasional mesangial and subepithelial deposits were also seen. In one patient, prominent subepithelial deposits led to the diagnosis of type III MPGN (mixed pattern of membranoproliferative and membranous glomerulonephritis). Organized annular, finely fibrillar, cylindric or immunotactoid structures, compatible with cryoglobulins could not be identified in the biopsy samples of any of the patients with MPGN.

The remaining six patients had chronic interstitial nephritis (patients 9 and 16), acute proliferative glomerulonephritis (patients 11 and 18), amyloidosis (patient 12) and granulomatous glomerulonephritis with interstitial nephritis (patient 8).

FSGS was not found in any of the 19 patients.

Discussion

In this report, we present data on a cohort of 19 patients with heroin addiction and significant proteinuria of unknown aetiology, with or without azotaemia, who had renal biopsies. One major finding was that all patients had serological evidence of HCV infection, whereas only one had HBV surface antigen and three were HIV positive. A second major finding was that the predominant pathologic lesion was MPGN, seen in 13 patients (12 with type I and one with type III). A third important observation was that, in the period under study (1993–2001), no decline was observed in the incidence of renal disease associated with heroin abuse.
### Table 3. Renal biopsy findings

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<th>Interstitial infiltration</th>
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*aC, crescents; A, amyloid.
bEM, electron microscopy.

Heroin has been associated with the occurrence of renal disease [12]. An increased risk for ESRD with an odds ratio of 19.1 was noted for users of heroin or other opiates when compared with non-users [12]. Several forms of renal involvement in heroin addicts have been described. They include FSGS (also known as HAN) [1], acute renal failure due to non-traumatic rhabdomyolysis, amyloidosis in subcutaneous heroin addicts, endocarditis-associated glomerulonephritis, hepatitis-related glomerulonephritis and HIV-associated focal glomerulosclerosis (also known as HIVAN) [9].

After the identification of HIV-associated focal glomerulosclerosis (HIVAN), this disease rapidly supplanted FSGS associated with heroin abuse (HAN) as the major renal disorder affecting drug addicts, and the incidence of HAN has declined dramatically. The basis for this decline is unclear. The possibility that HAN represents merely a form of HIVAN cannot be excluded, although HAN was already well characterized before the HIV era and it can develop in HIV-negative intravenous drug addicts.

Interestingly, both HAN and HIVAN sclerosing glomerulopathies have been observed predominantly in black patients. This is in good agreement with the fact that idiopathic FSGS, and especially its collapsing variant [13], have a striking predominance in black people. Renal diseases in general may also be more aggressive and rapidly progressive in black people than in other ethnic groups [14]. It has been suggested that genetic factors may play a role [14].

We were unable to find patients with FSGS in our cohort of Caucasian heroin addicts with nephropathy. Instead, the most frequent type of glomerular lesion found was MPGN associated with HCV infection.

HCV infection is highly prevalent among intravenous drug addicts, up to 95.7% of patients in some series [15], and is the primary form of chronic hepatitis found in intravenous heroin addicts. It must be noted that the prevalence of hepatitis C in the early studies of nephropathy associated with heroin abuse is unknown, since it was not identified as such, but rather as part of the non-A, non-B type of hepatitis. The association of MPGN with chronic HCV infection was first described in 1993 by Johnson et al. [16]. In their study, 50% of patients had a history of drug abuse and there were no black patients. The pathogenesis of HCV-associated MPGN is probably a result of glomerular deposition of circulating HCV and anti-HCV antibodies [16]. Treatment with interferon-α has been shown to improve proteinuria, suppress viraemia and stabilize renal function. However, patients often relapse after therapy is stopped [16].

Our findings are in accordance with some previous reports (Table 4). The association between heroin addiction and MPGN was first described in 1972 by Kilcoyne et al. [3], who reported renal biopsies in seven heroin addicts with nephrotic syndrome. MPGN with IgM and complement deposition was found in all patients. In 1988, Uzan et al. [17] described renal lesions in 13 European Caucasian heroin addicts: five had nephrotic syndrome, and renal biopsy showed various
types of glomerular disease but no cases of FSGS. Dettmeyer et al. [18] described 179 autopsies of European intravenous drug addicts: 61.7% had MPGN, but no case of FSGS were found. Even in African-American intravenous drug addicts co-infected with HCV and HIV, the development of immunocomplex glomerulonephritis might dominate the clinical course of the disease [19]. In 1997, Stokes et al. [19] described the clinical features and renal pathologic findings of 12 intravenous drug addicts, seven black and five Hispanic, co-infected with HCV and HIV: renal biopsy showed MPGN in five patients, mesangial proliferative glomerulonephritis in five, membranous nephropathy in one and ‘collapsing’ glomerulopathy with immune-complex deposits in one. In 1999, Cheng et al. [20] described the clinical pathological features of 14 intravenous drug addicts, 13 African-American and one Hispanic, co-infected with HCV and HIV: renal

Fig. 2. (A) Light microscopy: enlarged glomerulus, showing an increase in mesangial matrix, hypercellularity, lobulation and leucocyte infiltration (haematoxylin–eosin; magnification ×470). (B) Thickened and double-contoured capillary walls can also be appreciated (periodic acid–Schiff; magnification ×470). (C) Electron micrography: glomerular basement membrane splitting and subendothelial electrodense deposits (magnification ×25 000). (D) Immunofluorescence microscopy: granular peripheral capillary loop deposits of C3.
biopsies found MPGN type I or type III in 11 patients (79%) and membranous glomerulopathy with atypical features in three (21%), including overlap with collapsing glomerulopathy in one. The median time to dialysis or death in that series was 5.8 months. They concluded that co-infection with HIV in patients with HCV-associated glomerulonephritis leads to an aggressive form of renal disease that can be easily confused with HIVAN.

Two of our patients had main histological diagnoses of interstitial nephritis, but with associated glomerular lesions; which may have been responsible for the significant proteinuria that was found in them.

We conclude that FSGS (HAN) was not present in our cohort of Caucasian patients with renal disease and heroin addiction. The most frequent renal disease found was MPGN associated with HCV infection. This may be due to the high prevalence of HCV infection in heroin addicts. Although it is not possible to extend our conclusions to African-Americans, the designation ‘HAN’ must be re-evaluated, since it may be misleading and may imply a glomerulopathy unresponsive to therapy and rapidly progressive to ESRD. Our findings may have implications relevant to patient management and prognosis, including the need for precise characterization of renal histology in heroin addicts with significant proteinuria.

Conflict of interest statement. None declared.

References


Table 4. Previous descriptions of MPGN in intravenous drug addicts

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a: MPGN, membranoproliferative glomerulonephritis; HCV, hepatitis C virus; HBV, hepatitis B virus; HIV, human immunodeficiency virus.
b: F, female; M, male.
c: Post-mortem study.
ND, not done.