Renal injury due to hepatic hydatid disease

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Abstract

Background. Many studies on renal hydatid disease have been reported in the literature, and the disease process appears to be well defined. However, renal injury without direct renal invasion remains poorly understood. The present study aims to define the frequency and the property of the renal involvement in hydatid disease.

Methods. Eighty patients older than 18 years and diagnosed with liver echinococcosis were included in the study. The echinococcosis was diagnosed by the haemagglutination test and abdominal ultrasonography. Twenty-four-hour protein excretion was measured for patients who had elevated serum creatinine levels or whose urinalyses were positive for haematuria or proteinuria. Subsequently, renal biopsy was performed, and the specimens were examined by light microscopy and immunofluorescence staining.

Results. Haematuria was detected in 11 patients (13.75%), and proteinuria was detected in nine patients (11.25%). Percutaneous renal biopsy was applied to nine patients who gave signed consents to undergo the test. We detected four immunoglobulin A nephritis (together with tubulointerstitial nephritis in one patient), one membranoproliferative glomerulonephritis, one immunoglobulin M nephritis together with mesangiocapillary glomerulonephritis, one membranous glomerulonephritis, one amyloidosis and one tubulointerstitial nephritis. Renal hydatid cyst was detected only in four patients (5%).

Conclusions. Hydatid disease, which affects the kidney, is not rare, and we suggest that urinalysis and, if indicated, renal biopsy should be performed for hepatic hydatid disease diagnosis.

Keywords: glomerulonephritis; haematuria; hydatid cyst; proteinuria

Introduction

Renal disease has been described in various parasitoses, such as malaria, schistosomiasis and filariasis, especially in populations of endemic regions [1–3]. Parasitic nephropathies occur in three forms: acute renal injury caused by the systemic effects of severe infection, physical invasion by the parasite and renal injury caused by the host–parasite immune interaction [4]. The physical invasion by the parasite is the most common form. However, immune-mediated glomerular injury takes small part in the parasitic renal involvement, and there is no clear data on the incidence and prevalence.

Similarly, Echinococcus granulosus may cause renal injury [4]. Three forms of renal disease related to E.granulosus have been reported [4]. Renal hydatid disease is well defined, and many studies are present in the literature [5], but renal injury without direct renal invasion is a less well-known subject. There are only a few reported cases in the literature, and there is no case or investigational study revealing renal involvement as proven by biopsy. In the present study, we aim to put forward the frequency and the peculiarity of the renal involvement due to hydatid disease.

Material and methods

The study was approved by the local ethics committee and conducted in accordance with the ethical principles described by the Declaration of Helsinki. Patients older than 18 years and diagnosed with liver echinococcosis were included in the study programme. Eighty-six patients diagnosed with hydatid disease (admitted to the hospital between 2005 and 2009) were consecutively enrolled onto the study. Patients with a history of urinary system stones, renal or systemic disease such as vasculitis, collagen tissue disease or diabetes mellitus were excluded from the study. Eighty patients remained to populate the study cohort (Figure 1). After the symptomatic interrogation and physical examination, we performed
biochemical analysis of serum, complete blood count, abdominal sonography and chest roentgenography. The diagnosis of echinococcosis was established by the indirect haemagglutination test [6] and abdominal ultrasonography [7]. Twenty-four-hour protein excretion was measured for patients who had elevated serum creatinine levels or whose urinalyses were positive for haematuria or proteinuria. Subsequently, renal biopsy was performed, and the specimens were examined by light microscopy and immunofluorescence staining. All statistical analyses were performed using the SPSS for Windows, version 11.5 (Chicago, IL, USA). Unless otherwise stated, results were expressed as means ± standard deviation. P < 0.05 was considered statistically significant.

Results

The patients’ data have been given in Table 1. Eighty patients (32 males and 48 females; mean age 45.24 ± 16.42) with hydatid disease were included in the study. Renal hydatid cyst was detected only in four patients (5%). In ten patients (12.5%), serum creatinine levels were above the normal limit. Haematuria was detected in 11 patients (13.75%), and proteinuria was detected in nine patients (11.25%). In total, 12 patients (15%) had a sign of renal damage with unexplained aetiology, and renal biopsy was planned for them. Two patients refused renal biopsy and left the follow-up programme. One individual was

<table>
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<th>Table 1. Some features of the patients with liver echinococcosis</th>
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<tr>
<td>Age (year)</td>
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<td>Sex (M/F)</td>
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<tr>
<td>Duration of hydatid cyst (month)</td>
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<tr>
<td>Eosinophil (%)</td>
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<tr>
<td>Haematuria (n, %)</td>
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<td>Proteinuria (n, %)</td>
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<td>Impaired renal function (n, %)</td>
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<td>Lung cyst (n, %)</td>
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<td>Percutaneous drainage (n, %)</td>
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accepted as a patient with chronic renal disease because his renal dimensions were at atrophic levels. For this reason, renal biopsy was not applied to this patient. Nine patients consented to percutaneous renal biopsy, and it was applied to all of them (Figure 1). The patients' data and renal pathology results have been presented in Table 2. We detected four immunoglobulin A nephritis (IgAN) (together with tubulointerstitial nephritis in one patient), one membranoproliferative glomerulonephritis (MPGN), one immunoglobulin M nephritis (IgMN) together with mesangiocapillary glomerulonephritis (MCGN), one membranous glomerulonephritis (MGN), one amyloidosis and one tubulointerstitial nephritis (TIN).

Patient 1
She was diagnosed with MPGN and treated only with albendazole. Proteinuria returned to the normal range, and relapse did not occur.

Patient 2
She was diagnosed with TIN and treated by operation. Her renal functions recovered, and renal disease did not recur.

Patient 3
His renal biopsy was concordant with IgAN and vasculitis. He was treated with albendazole and by surgery. There was no relapse after treatment; however, renal functions worsened. For this reason, glucocorticoid (for 8 weeks) followed by cyclophosphamide (for 8 weeks) therapies were applied, but he did not respond to the immunosuppressive treatment. The patient's condition progressed to chronic renal failure. Thus, he has been undergoing peritoneal dialysis for 2 years.

Patient 4
He was diagnosed with IgAN and treated with albendazole. Renal functions and proteinuria returned to normal levels, and there was no relapse.

Patient 5
She was the only patient in our series diagnosed with amyloidosis. Albendazole and colchicine treatment was applied, but renal functions did not improve. She has been undergoing treatment for chronic renal disease.

Patient 6
He was diagnosed with IgAN and TIN. He was treated by surgery, and hydatid disease did not relapse. After the therapy, serum urea and creatinine levels returned to normal range; however, haematuria and proteinuria did not subside.

Patient 7
She had been diagnosed with hydatid disease 12 years ago. She was treated by surgery and albendazole three times. At the last examination, she still had hydatid disease. She was followed up, and her condition progressed to chronic renal failure (CRF). Thus, she has been undergoing haemodialysis.

Patient 8
She was diagnosed with IgMN and MCGN by renal biopsy. She was treated by surgery, and there was no relapse. Unfortunately, renal functions deteriorated, and proteinuria progressed.
Hydatid involvement of the kidney accounts for only 2–4% of all cases of hydatid disease [5,9,19], being the third organ site after liver and lungs. It generally remains asymptomatic for years, and the most frequent symptoms are pain, feeling of flank heaviness and dysuria [5]. The characteristic sonographic finding is anechoic lesions with well-defined margins. In the classification system of Gharbi et al., hydatid cysts are classified into five types on the basis of their sonographic appearance [7]. Surgery (drainage or obliteration of the cavity, cystopericystectomy or organ resection), chemotherapy (albendazole) and interventional procedures (percutaneous aspiration, injection and re-aspiration) are the therapeutic options. In many cases, conservative surgery is possible. However, one is well advised to use precaution, i.e. sterilize with albendazole before surgical treatment, and monitor serum titles of anti-Echinococcus antibodies. In our study, renal cyst proportion was detected slightly higher than what was previously reported [4,5]. It may be related to the small size of our study group. The members of the study group had no symptoms or signs, and their urinalysis and serum creatinine levels were normal (1.0 ± 0.2 mg/dL). We treated our cases of renal cyst with albendazole, and they appeared after a short time. Thereafter, surgical treatment was applied. Renal functions and proteinuria were resolved, and there was no relapse.

**Discussion**

Human liver echinococcosis is a parasitic zoonosis with intermediate (rodents, sheep, cattle and pigs) and final (carnivores) hosts. The latter can transmit the parasite to humans by their faeces, which are contaminated by the eggs of *E. granulosus*. Humans, infected from eggs, develop a highly infiltrative metacestode almost exclusively in the liver, which in late stages metastasizes to other organs [8].

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**Glomerular involvement due to immune complex deposition** has been described in echinococcosis. Albano Edelwiess and Lizardo-Daudt [10] investigated the effects of hydatidosis on the glomeruli of sheep. They observed glomerular cellular proliferation, thickening of the capillary wall and haematoxylin cylinders almost in all animals. Furthermore, mesangial and subendothelial granular echinococcoses were detected in all of them by immunofluorescence staining. These findings were revealed by electron microscopy as well. *Echinococcus* antigens against circulating antibodies were determined in the sera of sheep with echinococcosis. These findings were not detected in the control group. Besides, there are very few case reports of hydatidosis associated with glomerulonephritis in the literature. Mesangiproliferative nephritis [11–13], membranous glomerulopathy [14], minimal change disease [15] and IgAN [16] have been described. The role of hydatid antigen in the pathogenesis of glomerulonephritis was also documented in humans [13,14]. The host tends to eliminate the parasite by innate immune mechanisms, which principally include monocyte phagocytosis, induction of natural killer cells and complement activation via the alternative pathways [4]. Monocyte activation also leads to a cascade of acquired immune responses mainly initiated by activation of T-helper cells. This pathway is controlled by a number of monocyte-released interleukins including IL-1, IL-6 and IL-12 [4,17]. The immune-mediated parasitic nephropathy manifests some clinical conditions. It includes acute or progressive glomerular lesions, acute interstitial nephritis and amyloidosis. Hydatid cyst associated with glomerulopathies is generally acute, is self-limited or resolves after the treatment of hydatid disease [13,18,19]. However, there are too few chronic and progressive glomerulonephritis reported in literature [12,16]. In our series, most of the patients recovered after treatment. Nevertheless, Patient 4 (IgAN and vasculitis) and 5 (amyloidosis) developed progressive glomerulonephritis and chronic renal disease. Furthermore, CRF was detected in Patient 7 which may be related to the relapsing hydatid disease because her renal functions were normal before the hydatid disease and she did not have any clear aetiological factor for CRF. Unfortunately, because of the insufficient data, it is not possible to predict which factors affect the disease progression. Rincon et al. [12] reported a case of MCGN associated with hydatid disease in an elderly man. His clinical findings were consistent with nephrotic syndrome, and he did not respond to the therapy. His condition had progressed to the end stage of renal failure. Patient 8 showed a similar outcome, but our case did not show nephrotic syndrome, and IgMN was detected in her in addition to MCGN. Our patient’s condition had also progressed to chronic renal disease, and conservative therapy was applied to her.

To our knowledge, no clinical association has yet been reported between hydatid disease and IgM nephritis. However, IgM deposition at renal mesangium and capillary wall due to parasitic infestations was demonstrated in humans and experimental animal models. Leishmaniasis [20], schistosomiasis [21], Chagas’ disease [22] and malaria [23] are the most common diseases associated with IgM nephritis. It may be suggested that immune-mediated mechanisms are also responsible for hydatid disease-associated IgM nephropathy as hydatid cyst-associated IgA nephritis.

Many parasites may cause MPGN. For example, el-Shoura reported MPGN with abnormal deposits during the acute infection with the malaria parasite [24]. Also, the amount and density of the immune complex deposits could be correlated with the degree of parasitaemia in their report. Albano Edelwiess and Lizardo-Daudt had reported immune complex-mediated membranoproliferative glomerulonephritis associated with hydatid disease in sheep [10], but there was no case study of MPGN in human echinococcosis. For this reason, our Patient 1 may be an important model for future cases of hydatid disease associated with MPGN.

TIN was detected in two patients in our study (Patient 2 and 6). The two patients were investigated for the TIN aetiology. Neither of the patients had any history of current systemic diseases, drug usage nor acute or chronic infection. For this reason, we thought that TIN was associated with
the hydatid disease. Furthermore, the laboratory findings related to TIN returned to normal after the hydatid cyst treatment in Patient 2. Although both patients were similar in age, serological titre of the echinococcosis and hydatid disease process, Patient 2 did not recover after the treatment. As a result, Patient 2 had a mild damage in renal function (serum creatinine was 2.9 mg/dL, and proteinuria was 1010 mg/day) and had no any glomerular pathology. However, Patient 6 had TIN together with IgAN, and his protein excretion was higher than Patient 2 (5768 mg/day). There is no report of the tubulointerstitial nephritis associated with echinococcosis in the literature. Besides, parasite-associated interstitial nephritis had been described for a few parasitoses, Leishmania donovani and Schistosoma mekongi [25,26]. Monocytes and lymphocytes infiltrate the renal interstitium due to acute inflammation [25]. Acute tubular necrosis is seen with some parasitic infections, and it is associated with acute interstitial nephritis [4]. The main pathologic mechanism of tubular necrosis described for malaria is massive monocyte activation [27]. The effect of parasitic agent on the monocytes leads to a cascade of mediator release such as septic shock. This leads to peripheral blood pooling, reduction of the effective blood volume and haemoconcentration. Diminished renal perfusion becomes exaggerated. We suggest that a similar mechanism may be responsible for renal disease of echinococcosis.

Similar to some parasitic infections, echinococcosis can lead to amyloidosis [4,28,29]. In our study, only one patient was diagnosed with amyloidosis. He had high level of proteinuria, and his renal function had deteriorated. He did not benefit from treatment, and his condition progressed to the end stage of renal failure. The mechanism of the parasitic amyloidosis can be explained as the parasitic antigens induced the release of IL-1 and IL-6 by monocytes. These interleukins stimulate the hepatocytes to release AA protein. Impaired function of monocytes leads to insufficient clearance of this protein, thereby increasing its circulating blood level and the collected material deposited in vascular and glomerular structures [4,29].

In conclusion, we observed the prevalence of biopsy-proven hydatid nephropathy, and we did not find any related factors for renal disease. Furthermore, we described the first cases of the TIN, IgM nephropathy and MPGN associated with hydatid disease. We demonstrated that the hydatid disease, which affects the kidney, is not rare, and we suggest that urinalysis and, if indicated, renal biopsy should be performed for patients suspected with hepatic hydatid disease.

References


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