JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Brief Original Article

Pancreatitis in patients with hemorrhagic fever with renal syndrome: A five-year experience

Edmond Puca[1], Arjan Harxhi[1], Pellumb Pipero[1], Elda Qyra[1], Gentian Stroni[1], Ermira Muco[1], Zhenisa Hysenaj[1], Elvana Rista[2], Gjok Tosku[3], Silvia Bino[4]

[1] *Service of Infectious Diseases, University Hospital Center, Tirana, Albania*
[2] *Service of Nephrology, Hygeia Hospital, Tirana, Albania*
[3] *Service of Radiology, University Hospital Center, Tirana, Albania*
[4] *Institute of Public Health, Tirana, Albania*

Abstract

Introduction: Pancreatitis is a rare complication of hemorrhagic fever with renal syndrome (HFRS). The causative agents of HFRS are hantaviruses, which belong to the genus *Hantavirus*, family *Bunyaviridae*. The purpose of this study was to evaluate cases of acute pancreatitis (AP) in patients with HFRS at the Service of Infectious Diseases, Tirana, Albania.

Methodology: In this retrospective study, clinical and laboratory data was obtained from 36 patients with confirmed HFRS, between January 2011 and December 2016. The diagnosis had been confirmed by a positive enzyme-linked immunosorbent assay (ELISA) for IgM or IgG antibodies to hantavirus.

Results: The average patient age was 39.7 ± 14.1 years with a range of 15-59 years. From 36 HFRS patients, four (11.1%) were found to have AP, all were male. Abdominal pain was the most common symptom and an increase in amylase and lipase was observed in all four patients. Abdominal computed tomography (CT) indicated pancreatitis with surrounding edema, necrosis and hemorrhage. In this study, the total mortality was 11.1% (4/36), while mortality in patients with AP was 25% (1/4).

Conclusions: The results indicate that AP is a serious complication of HFRS, with a poor prognosis. Increased awareness of AP in clinicians and assessment of amylasemia or lipasemia in patients with HFRS should be considered, especially in endemic areas where a rapid diagnosis is crucial for a positive outcome.

Key words: hemorrhagic fever with renal syndrome; hantaviruses; Dobrava virus; pancreatitis.

J Infect Dev Ctries 2017; 11(11):900-903. doi:10.3855/jidc.9567

(Received 05 July 2017 – Accepted 10 October 2017)

Introduction

Hemorrhagic fever with renal syndrome (HFRS) is an endemic disease in Europe as well as in Asia. The causative agents of HFRS are hantaviruses, which belong to the genus *Hantavirus*, family *Bunyaviridae*, the most common are: Hantaan virus (HTNV), Amur virus (AMV), Seoul virus (SEOV), Dobrava virus (DOBV), and Puumala virus (PUUV) [1–3]. Hantaviruses cause two diseases, typified by HFRS in Eurasia and hantavirus cardio-pulmonary syndrome (HCPS) in the Americas. Hantaviruses are usually transmitted to humans through aerosolized excrements from rodents, rodents are assymptomatic carriers with lifelong infections [1–4]. The physiopathology of hantavirus infection is not completely understood, however capillary endothelium injury occurs which increases vascular permeability. Endothelial cells and monocytes are thought to be the primary viral targets but infection does not appear to have direct cytopathic effects. The main factor that determines the course and severity of HFRS is the degree of increased permeability of infected endothelium [3,5,6]. As a systemic pathology, HFRS can affect various systems in the body. The most common symptoms in patients with HFRS are fever, sweating, myalgia, lumbago, nausea and vomiting, headache, abdominal pain, blurred vision and oliguria, which is followed by polyuria in patients with a good prognosis [3,4,7,8]. The most commonly affected organ is the kidneys but other organs, such as the lungs, liver, heart, central nervous system, endocrine centers and gastrointestinal tract, may also be affected [7–9]. One of the most serious extrarenal injuries of HFRS, in terms of the gastrointestinal system, is acute pancreatitis (AP) [4–10]. AP has a serious pathology, with rapid clinical presentation which has been

associated with high mortality [7]. According to Fan *et al*., 2013, AP is the result of direct attack of hantavirus on the pancreas; therefore, the management of pancreatitis, as well as treatment of primary disease, should be performed simultaneously [5]. Reports of AP as a complication of HFRS are limited and variable. The purpose of this study was to evaluate AP as a complication of HFRS in Albania, and to raise the awareness of clinicians from endemic regions to the presence of this pathology.

Methodology

In this retrospective study, patients diagnosed with HFRS admitted to the Service of Infectious Diseases, University Hospital Center, Tirana, Albania between January 2011 and December 2016, were included in the study. The selection was made based on clinical data suggestive for HFRS, which was subsequently confirmed by a positive enzyme-linked immunosorbent assay (ELISA) for IgM or IgG antibodies (Ab) to hantavirus. Clinical and laboratory data were collected. The diagnosis of AP was based on clinical data, laboratory results and radiological imaging. The diagnosis of AP requires the presence of two or more of the following criteria: (1) abdominal pain consistent with AP; (2) increased level of serum lipase or amylase - at least three times greater than the normal range or; (3) characteristics of AP by radiological imaging (CT-scan, magnetic resonance imaging (MRI) or transabdominal ultrasonography (US)) [11].

Results

A total of 36 patients were diagnosed with HFRS in the Service of Infectious Diseases, University Hospital Center of Tirana, during a 6-year period. All patients had positive ELISA results for both IgM and IgG Ab to hantavirus. These patients included 32 males and 4 females (ratio M:F = 8:1). The average age was 39.7 ± 14.1 years, with an age range of 15-59 years. Most cases were reported during the period between June and August [9]. The first reported symptom in all patients was fever and all patients had the typical presentation of HFRS with acute renal failure. A total of four (11.1%) of the HFRS patients were diagnosed with AP, all were males between 32 and 59 years. Abdominal pain and fever were the dominant symptoms of these patients and abdominal pain was present from the first to the fifth day. The delay from the first clinical symptoms to development of AP symptoms was 4.5 days. All patients had amylase and lipase values increased threefold compared to the normal range. The mean value of amylase and lipase in patients without AP (32/36) was 64.8 mg/dL and 32.4 mg/dL, respectively. The average platelet concentration for all AP patients was 47750/μL (value for non AP patients = 150000-400000/μL). All patients with AP had fever, lumbago, oligoanuria, abdominal pain, nausea and vomiting. Thrombocytopenia was present in all patients who developed AP, but only one patient had hemorrhagic symptoms. In this study, the total mortality was 11.1% (4/36), while mortality in patients with AP was 25% (1/4). The difference in fatality rates between the HFRS groups with AP and without AP did

Table 1. Examination parameters for patients with acute pancreatitis.

	Patient 1	Patient 2	Patient 3	Patient 4
Gender	Male	Male	Male	Male
Age	53	37	32	39
Fever	Yes	Yes	Yes	Yes
Nausea/vomiting	Yes	Yes	No	Yes
Headache	Yes	Yes	No	Yes
Abdominal pain	Yes	Yes	Yes	Yes
Platelet count	23000/μL	48000/μL	56000/μL	64000/μL
Amylase (normal range = 28-100 mg/dL)	420	480	327	840
Lipase (normal range = 25-65 mg/dL)	156	242	207	364
Oliguria	Yes	Yes	Yes	Yes
Lumbago	Yes	Yes	Yes	Yes
Urea (mg/dL)	158	120	87	154
Creatine (mg/dL)	5.3	4.2	3.9	4.1
Mortality	No	No	No	Yes
Comorbidities	Yes	No	No	No

not reach statistical significance (p-value = 0.348501) due to the small sample size. Sociodemographic data and laboratory results of patients who developed AP are presented in Table 1.

Discussion

HFRS is a disease endemic in many countries and has distinctive clinical manifestations throughout the disease course, from acute influenza-like febrile illness to severe disease. Common clinical manifestations of HFRS are: fever, myalgia especially lumbago, hypotension, hemorrhagic phenomena and renal insufficiency. The key feature is renal involvement; however, several extra-renal manifestations have also been reported. As reported elsewhere, males have predominance compared to females [2,3,5,10], in this study the M:F ratio was 8:1. AP was observed with HFRS progression in approximately 10% of cases in this study. Other reports indicate that AP develops in 2.8% to 54% of patients with HFRS depending on geographic location [8–10]. This is the first Albanian study that presents the frequency of AP as a complication of the HFRS, however a case report of AP in a patient with HFRS in Albania has been previously published [4]. All patients with AP experienced abdominal pain as the main symptom, fever, nausea and vomiting were also observed. The time span from the first clinical symptoms to AP diagnosis was 4.5 days. The delay in diagnosis highlights the fact that AP is a poorly recognized complication of HFRS with a variable clinical course based on its pathophysiology. However, the aggressiveness of AP is associated with the viral agent. Increased vascular permeability is key to pathogenesis of hantavirus infection whereby capillaries become engorged and focal hemorrhages develop. Ultimately, the systemic expansion of capillary leakage leads to retroperitoneal edema which may affect the pancreas. Interestingly, the pancreas appeared unremarkable upon gross examination but microscopic examination revealed mild interstitial hemorrhage and vascular congestion [3,6,10]. We speculate that this is a mechanism of acute pancreatitis in HFRS. In Albania, the major causative hantavirus agent is Dobrava-Belgrade virus (DOBV). At least three DOBV genotypes have been identified, in association with *Apodemus flavicollis*, *A. agrarius* and *A. ponticus* hosts, DOBV associated with *A. flavicollis* has been found to be more pathogenic with a fatality rate up to 12% [12–14]. According to Papa *et al*., 2016, DOBV is the only hantavirus detected in Albania and *A. flavicollis* was the only DOBV-positive rodent species [12,13,15]. HFRS caused by this virus has a poorer clinical course compared to the other viruses. We speculate that systemic infection could be connected with the presence of DOBV in the human intestine which could explain the clinical phenotype of severe gastrointestinal symptoms.

However, our investigation was limited (only 36 patients in six years). Diagnosis of AP is not challenging, however, in this study it took 1.5 to 2 days to establish an AP diagnosis after the first symptoms manifested. Although AP is infrequent in HFRS patients, it should be considered if patients with fever and acute renal insufficiency have abdominal pain, especially in the epidemic areas of HFRS. In addition, when HFRS patients present with abdominal pain, pancreatic enzymes should be assessed and imaging conducted to assess the pancreatic function and investigate AP. As a disease with a rapid onset, early diagnosis may be a prognostic factor for AP management. Mortality in patients with AP in this study was 25% (1/4), compared with overall mortality in HFRS which was 11.1%. The HFRS mortality was consistent with other studies [16]. Our study indicates that pancreatic enzymes should be monitored in HFRS patients with abdominal pain, especially in those patients with constant upper abdominal pain radiating to the back.

Conclusions

Generally, patients with HFRS complain of lumbar pain, so the clinician should remain aware of the potential for abdominal pain caused by AP. Laboratory tests and radiological examination can assist in the diagnosis of AP which is a serious complication of HFRS, leading to poor prognosis and outcome. A clinical awareness and monitoring of amylase or lipase in patients with HFRS may be important, especially in endemic areas where a rapid diagnosis can be the crucial factor for a positive outcome. The immediate initiation of supportive therapy may lead to a better outcome and reduced complications.

References

1. Vilibic-Cavlek T, Furic A, Barbic L, Tabain I, Stevanovic V, Mlinaric-Galinovic G (2017) Clinical and virological characteristics of hantavirus infections in a 2014 Croatian outbreak. J Infect Dev Ctries 11: 73–80. doi: 10.3855/jidc.7987.
2. Rista E, Pilaca A, Akshija I, Rama A, Harja E, Puca E, Bino S, Cadri V, Kota M, Nestor T, Arjan H (2017) Hemorrhagic fever with renal syndrome in Albania. Focus on predictors of acute kidney injury in HFRS. J Clin Virol - 91: 25–30.
3. Jiang H, Du H, Wang LM, Wang PZ, Bai XF (2016) Hemorrhagic fever with renal syndrome: pathogenesis and clinical picture. Front Cell Infect Microbiol 6: 1.

4. Puca E, Pilaca A, Pipero P, Kraja D, Puca EY (2012) Hemorrhagic fever with renal syndrome associated with acute pancreatitis. Virol Sin 27: 214–217.
5. Fan H, Zhao Y, Song FC (2013) Acute pancreatitis associated with hemorrhagic fever with renal syndrome: clinical analysis of 12 cases. Ren Fail 35: 1330–1333.
6. Kitterer D, Artunc F, Segerer S, Alscher MD, Braun N, Latus J (2015) Evaluation of lipase levels in patients with nephropathia epidemica--no evidence for acute pancreatitis. BMC Infect Dis 15: 286.
7. Bui-Mansfield LT, Torrington KG, Kim T (2001) Acute pancreatitis in patients with hemorrhagic fever with renal syndrome. Mil Med 166: 167–170.
8. Park KH, Kang YU, Kang SJ, Jung YS, Jang HC, Jung SI (2011) Experience with extrarenal manifestations of hemorrhagic fever with renal syndrome in a tertiary care hospital in South Korea. Am J Trop Med Hyg 84: 229–233.
9. Kang ES, Lee S, Kim W, Park SK, Lee PW, Kang KP, Kang SK (2005) Acute pancreatitis associated with haemorrhagic fever with renal syndrome. Nephrolony (Carlton) 10: 421–422.
10. Zhu Y, Chen YX, Zhu Y, Liu P, Zeng H, Lu NH (2013) A retrospective study of acute pancreatitis in patients with hemorrhagic fever with renal syndrome. BMC Gastroenterol 13: 171.
11. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, Tsiotos GG, Vege SS; Acute Pancreatitis Classification Working Group (2013) Classification of acute pancreatitis - 2012: revision of the Atlanta classification and definitions by international consensus. Gut 62: 102–111.
12. Papa A, Rogozi E, Velo E, Papadimitriou E, Bino S (2016) Genetic detection of hantaviruses in rodents, Albania. J Med Virol 88: 1309–1313.
13. Rogozi E, Bego F, Papa A, Mersini K, Bino S (2013) Distribution and ecology of small mammals in Albania. Int J Environ Health Res 23: 258–268.
14. Avšič Županc T, Korva M, Markotić A (2014) HFRS and hantaviruses in the Balkans/South-East Europe. Virus Res 187: 27–33.
15. Papa A (2012) Dobrava-Belgrade virus: phylogeny, epidemiology, disease. Antiviral Res 95: 104–117.
16. Sibold C, Ulrich R, Labuda M, Lundkvist A, Martens H, Schütt M, Gerke P, Leitmeyer K, Meisel H, Krüger DH (2001) Dobrava hantavirus causes hemorrhagic fever with renal syndrome in central Europe and is carried by two different Apodemus mice species. J Med Virol 63: 158–167.

Corresponding author
Edmond Puca, PhD
Department of Infectious Diseases, University Hospital Center, Tirana,
Rruga e Dibres, No 370, 1007, Tirana, Albania
Phone +355684062820
Email: edmond_puca@yahoo.com

Conflict of interests: No conflict of interests is declared.