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The Risk of Severe Acute Kidney Injury Requiring Renal Replacement Therapy in Viral Hemorrhagic Fevers. A Review of Literature

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Abstract

Objective: It demonstrates the correlation of the viral hemorrhagic fever with kidney failure and the treatment as well as the outcome. Method: A PubMed search of the English literature from 1999 to 2019 was performed using "viral hemorrhagic fever, Case Report, Renal Failure" as the subject. The inclusion criteria were the following: 1) case report and case series of two or more patients; 2) the report detailed the clinical presentation and reported the status of the renal system; 3) the report described the management of renal failure if any; and 4) the etiology of the infection is known and is one of the known agents of viral hemorrhagic fever, listed on the centers of disease control website. We excluded infections related to vaccination related to viral hemorrhagic fever. Result: We found the mean age of these patients was 41.5. The male to female ratio was about 3.5:1. Dengue and Hantaviruses constituted 70.5% of patients. The overall mortality of the study cohort was 32.2%. Half of the patients had acute kidney injury and required renal replacement therapy. The chi-square statistic is 0.41; The *p*-value is 0.51; The chi-square statistic is 6.4254. Overall mortality was 32.3% in one cohort of 78 patients. The illness goes through several stages [1] [2] of clinical features and some viruses in the group have a high case fatality rate. Conclusions: Early diagnosis with aggressive supportive care is critical for improving clinical outcomes. Renal involvement is common. Amongst the cohort reviewed, of patients who had acute kidney injury, half of the patients required renal replacement support. However, some viruses cause greater kidney injury than others, for instance, kidney injury is more severe in Dengue hemorrhagic fevers when compared to Hantaviruses. Simultaneous management of public health by prevention and control of outbreaks is particularly important.

Keywords

Acute Kidney Injury (AKI), Renal Replacement Therapy, Viral Hemorrhagic Fevers

1. Background

Viral hemorrhagic fevers (VHFs) are severe infections caused by a group of viruses belonging to several families. These infections are characterized by severe, multi-organ involvement with a high mortality rate. Acute kidney injury is often a component of the multisystem syndrome that includes involvement and dysfunction of the central nervous system, pulmonary, cardiovascular system, hematopoietic system, gastrointestinal system and liver. Renal replacement therapies (RRT) are often needed. We reviewed the literature to retrospectively study the extent to which RRT is utilized if there is any relationship between the use of RRT and mortality.

2. Methods

To assess whether and to what extent, published studies report acute kidney injury (AKI) requiring supportive renal replacement therapy (RRT) during viral hemorrhagic fever (VHF). A PubMed search of the English literature from 1999 to 2019 was performed using "viral hemorrhagic fever, Case Report, Renal Failure" as the key words. A manual search of the bibliographies of retrieved articles was also added. As a result, we reviewed over two hundred articles in detail. The inclusion criteria were the following: 1) Case report and Case series of two patients; 2) The report detailed the clinical presentation and reported the status of the renal system; 3) the report described the management of renal failure if any; and 4) the etiology of the infection is known and is one of the known VHF listed on the centers of disease control (CDC) website. We excluded infections related to vaccination related to VHF. 74 publications met the inclusion and exclusion criteria that reported 78 patients. The following data was collected from the eligible publications; 1) demographic data; 2) geographic data; 3) presenting symptoms; 4) the presence or absence of renal failure; and 5) the need for renal replacement therapy.

2.1. Statistics

Descriptive statistics and analytic statistics were conducted using a statistical calculator package available online at https://www.socscistatistics.com/tests. Age was presented as mean and interquartile range. Chi Square values were calculated and p-value of <0.05 was considered significant.

2.2. Results

There were 74 publications and 78 patients included in the study. All these pa-

tients were reported to have AKI. The mean age of these patients was 41.5 (IQR, 24). The male to female ratio was about 3.5:1. The Dengue and Hantaviruses constituted 70.5% of patients. Other viruses that constituted the remainder of the causes were puumala virus, Seoul virus, Ebola virus, yellow fever, Lassa fever virus etc. Overall mortality of the study cohort was 32.2%. Half of the patients who had AKI required RRT. Comparing patients who survived to those who died, there was no difference in the need for RRT. The chi-square statistic is 0.41 The p-value is 0.051; Not significant at $p < 0.05$. However, the need of RRT was etiology dependent. Hantavirus infections were less likely to require RRT when compared to Dengue and the group of Other viruses. The chi-square statistic is 6.4254. The p-value is 0.01. Significant at $p < 0.05$.

3. Discussion

3.1. Definition

VHFs causing viruses are listed on the CDC website (1). These viruses belong to several groups of viral families causing severe multisystem illness leading to failure and insufficiency of multiple end organs simultaneously. The mortality rates vary from 20% - 40% and in our cohort the mortality rate was 32.2%. These viruses can be divided into those which are classified as biosafety level four 4 (BSL-4) pathogens and those which are non BSL-4. The two non BSL-4 viruses cause Dengue and Yellow fever.

3.2. Epidemiology

These viruses are worldwide and each virus has a niche geographic location. Frequently travelers from one location to another may transport these viruses outside of the usual distribution. Hence the history of travel is important in the diagnosis of VHFs.

All continents except Antarctica are home to an endemic virus or viruses. For example, Dengue virus is frequent in Asia, Puumala virus in Europe. Dengue and the Hantaviruses are frequently most common amongst these viruses causing severe infections. In our cohort dengue and Hantaviruses accounted for 70% of the cases. Males are more frequently affected than females and this could be due to exposure to outdoors the vectors. The mean age in our cohort was 41.5 years with IQR (1 - 2) of 24.

3.3. Etiological Agent

The viruses causing VHFs belong to the following families and are mostly zoonosis; 1) Arenaviridae, 2) Bunyaviridae, 3) Flaviviridae, and 4) Filoviridae. All are enveloped, single stranded RNA viruses. The largest family is the Bunyviridae with over 300 viruses; Hanta viruses belong to this group. Arenaviridae have their single strand RNA bi segmented. Arenaviruses are classified as the New World viruses and the Old World or LCM/Lassa complex. The Ebola virus belongs to the Filoviridae family and this family is largely found in the African

continent. Ebola and Marburg viruses belong to this group. Flaviviridae has positive sense RNA while the other three families named above have negative sense RNA. Flaviviridae includes Dengue Fever, Yellow fever, Japanese encephalitis, West Nile and Zika viruses.

4. Pathophysiology of AKI in VHF

Acute kidney injury in viral hemorrhagic fevers is multifactorial, most of these diseases are endemic in resource limited countries, therefore, most of the data has been obtained through cases reports, and case series, AKI varies as well upon the moment of the course of the disease, *AKI's dengue fever* has been associated with, acute tubular necrosis, hemolytic uremic syndrome, proteinuria, glomerulopathy and nephrotic syndrome [3]. Direct cytopathic effect of the viral protein on the glomerular and tubular cells, tissue injury caused by immune complexes composed of viral antigens with antiviral antibodies, causing damage through inflammatory mediators which are released in response to the glomerular or tubular cytopathic effects of the viral antigens [4] [5] [6] Other causes of AKI in dengue fever are rhabdomyolysis [7] [8] [9] [10] [11], Hemodynamic instability, some cases with hemolytic uremic syndrome which is not well understood pathophysiology [12] [13] [14].

Hantavirus AKI mechanism is not well understood, studies have shown, damage of the podocytes, tubular epithelial and glomerular endothelial cells revealed disturbances in structure and integrity of cell to cell contacts, observed by redistribution and reduction of the light junction protein ZO-1 along with decreased transepithelial resistance in infected epithelial monolayers [15], There seems to be a relationship between human leukocyte antigen (HLA) haplotypes in the severity of the disease [16] [17], and T-cell mediated immune response. It is supported by the observed elevated CD8+ cell count. Furthermore, the principal characteristic described is the increased vascular permeability without apoptotic damage to the capillary endothelium, suggesting the likely breakdown of endothelium due to cytokine release, which means the insult and damage is immunological rather than anatomical to the endothelium and is reflected by the scarcity of renal lesions on kidney biopsies [18] [19] [20].

Ébola virus and Marburg virus are two of the more lethal diseases and both of them course with a high renal involvement and normally require RRT as part of the management, the AKI is caused due to systemic inflammatory response syndrome and capillary leakage, associated with massive fluid loss from vomiting and severe diarrhea, which lead to pre-renal azotemia [21], renal ischemia causing acute tubular necrosis (ATN), cytokine storm, superinfection with bacterial pathogen [21], Ebola virus has been shown to infects renal tubular cells, clothing abnormalities [20] [21].

The rest of the hemorrhagic viruses share characteristics in common with the previous ones, volume depletion, prerenal azotemia, kidney cell compromise, and the need for RRT as part of management.'

5. Risk Factors

See Table 1.

Clinical features: The incubation period for VHFs ranges from 2 to 21 days. Patients initially have a high fever, headache, tiredness, joint aches, muscle aches, nausea, abdominal pain, and non-bloody diarrhea that usually last about a week. High fever is an early sign, abrupt in onset, associated with headache and myalgias with exception of arenaviruses, where the fever and illness is more gradual in onset. Multisystem involvement is noted from the very early phase however the severity may vary in individuals. Capillary leak and endothelial dysfunction are the hallmarks of VHFs.

We found 78 severely affected patients, all of whom had AKI, 50% required renal support. Rhabdomyolysis occurred in 8 of the 78 patients and most likely caused acute tubular necrosis (ATN).

Gastrointestinal involvement is common in the form of nausea, vomiting, abdominal pain and diarrhea and was reported in 58% of the patients; which most likely caused pre renal AKI; however there could be other mechanisms of AKI but kidney biopsy was not frequently done.

Nervous system involvement in the form of headache, confusion, loss of consciousness or visual changes are seen in over half the patients with VHFs. Forty patients from our cohort (N = 78) [3] [12] [13] [14] [22]-[39] had some CNS involvement.

There were no clinical features in this cohort, with advanced disease, that was predictive of death. The use of RRT was also not different between the group that recovered and the group that succumbed to the disease. Although Hanta viruses can cause Renal syndrome, the proportion of patients requiring RRT was significantly less when compared to Dengue or Other viruses causing VHFs.

In advanced stages, confusion, hypotension, respiratory failure, nephrogenic edema, liver failure are noted. Imaging can show pulmonary infiltrates, and pleural effusions. EKG may show tachycardia, relative bradycardia, and conduction abnormalities.

Deep bleeding in the form of intracerebral bleeding, gastrointestinal bleeding, perirenal hematomas, genitourinary bleeding may be noted but is seldom life threatening and is noted in less than 10% of patients (6.5% in this cohort).

6. Diagnosis

The diagnosis of viral hemorrhagic fever is variable, first at all it is made in based

Table 1. Risk factors.

	Bunya	Arena	Filo	Flavi
Reservoir	Rodents	Rodent	Bat (UK)	Monkeys
Risk factor	Contact with rodent urine	Contact with Rodent excreta		Contact with ticks
Arthropod borne	No	Yes	UK	Yes
Person-to-Person	Yes	Yes	Yes	Yes

on clinical manifestation, however we have under our dispositions certain studies available: Virus Culture, Electron Microscopy, Nucleic Acid Detection, Immunohistochemistry, serology studies, etc. In our cohort diagnosis was defined as less than 3 days as enough time to make it, and only 54% made it in the period of time, 87% were made during the hospital admission.

61% of the diagnoses were made with seroogy studies, the combination of serology studies and RT-PCR (Reverse transcription polymerase chain reaction) were 14%. Serology studies, it is an easy diagnostic tool and faster to perform, and is under the possibility of performing in developing countries as well as underdeveloped countries. The PCR becomes the diagnosis preference of Ebola virus.

7. Therapy

In the context of hemorrhagic fever, there is a limited specific treatment for each virus. The treatment for hemorrhagic viral fever is principal just support and management of the complications that can result in lethal outcome.

We found the principal treatment was supported 0.83%, with hemodialisis, plasma, blood, erythrocytes, cryoprecipitate transfusion, and mechanical ventilation. Bleeding was identified in only 5 of the 78 patients (6.4%). However, along with support management 37% of the cases were managed with antibiotics empirically due to possible bacterial infection, treatment that was discontinued later when the diagnosis was confirmed, just 8.9% was treated with antiviral specific treatment and that cases were Ebola, Marburg, Crimean-Congo virus.

It is important made a mention of the specific antibiotic treatment for bacterial infections as result of hospital related infection due to prolonged admission, magament (Mechanical ventilation) or diseases at the same time (Dengue plus Malaria), in our cohort we found this causality It constitutes 14%, as well as the 46% did not received specific or empirical treatment as we mentioned it before.

An important part of all the management due to all this virus have the potential of causes bleeding ones more than other, and the management is base in which is the deficit or the clinical manifestations, in our cohort with found the 0.30%, the quantity of each packed used it, is variable but we can assure the cases in which we used it more are the cases as Ebola, Marburg, Crimean-Congo virus.

8. Prognosis

The prognosis seems to be related on which type of hemorrhagic fever it is, based in the Dengue and Hantaviruses constituted 70.5% of patients, the mortality rate in this specific cohort was 24%, the most lethal virus are the virus that proceed from African continent: Ebola, Marburg, Crimean-Congo virus, and Lassa virus, given the few cases that we have of this hemorrhagic fever associated with renal damage the mortality is over come at least 100% or more. The mortality between dengue virus was 21% and between hantavirus it was 13%. The worse prognosis and outcome related to sex was 16 male again 3 Female, that is

mean 84% were men.

9. Prevention

The prevention of each disease related with virus is related with the disponibility of vaccines that with have, and for the moment there are scarce vaccines for management of this diseases, recently the WHO approve the vaccine for dengue virus and lassa virus, and experimental vaccines for the other virus are in process or are being tested in the population, therefore the prevention it is confined to avoid the contact with source for example uses it of repellents, avoid travel to areas with a high prevalence.

The prevention of lethal outcome when the disease is ongoing mostly is based in support management as we discussed before in this cohort.

10. Conclusion

VHFs are serious diseases. Overall mortality was 32.3% in one cohort of 78 patients. The illness goes through several stages (3 - 5) of clinical features and some viruses in the group have a high case fatality rate. History of travel, knowledge of epidemiology, recognition of clinical syndrome are important for early diagnosis. Early diagnosis with aggressive supportive care is critical for improving clinical outcomes. Renal involvement is common. Amongst the cohort reviewed patients who had acute kidney injury, half of the patients required renal replacement support. However, some viruses caused greater kidney injury than others for instance, kidney injury is more severe in Dengue hemorrhagic fevers when compared to Hantaviruses. Simultaneous management of public health by prevention and control of outbreaks are particularly important.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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