

Hemorrhagic Fever With Renal Syndrome and Its History in Iran

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Hemorrhagic fever with renal syndrome (HFRS) is a serious human disease of zoonotic viral origin. A group of different viruses that belong to the family of hemorrhagic fever could represent with HFRS. The basic pathophysiologic feature is virus-induced leaky microcirculation. There is no effective antiviral treatment against them. Because of rapid environmental changes, global warming, and increased global traveling, different hemorrhagic fever syndromes could be found anywhere in the world and beyond their old endemic borders. This review is a brief overview of HFRS in Iran during the early and mid-twentieth century.

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INTRODUCTION

Hemorrhagic fever with renal syndrome (HFRS) is caused by different viruses from diverse zoonotic RNA viruses families including *Flaviviridae*, *Bunyaviridae*, *Arenaviridae*, and *Filoviridae*.¹ They are transmitted by arthropods. Rodent-associated viruses transmit directly to vertebrates by infectious excreta or secretions. There are 4 clinical syndromes associated with these viruses: fever and myalgia, arthritis and rash, encephalitis, and hemorrhagic fever. These categories often overlap in the clinical syndromes that they are creating.¹

The viral HFRS is a condition of decreased vascular integrity, increased permeability, and shock. When it is accompanied with thrombocytopenia, it could lead to sever local and diffuse hemorrhage. Specific organs may be particularly impaired by some viruses, such as the kidneys in HFRS, the lungs in hantavirus pulmonary syndrome, and the liver in yellow fever.¹

Hemorrhagic fever with renal syndrome caused by Hantaan, Dobrava, Puumala (genus *Hantavirus* viruses and family *Bunyaviridae*) has a worldwide distribution, depending on rodent reservoir. Hantavirus pulmonary syndrome is mainly seen in America. Marburg and Ebola hemorrhagic fever

(*Filoviridae* family) are mainly limited to Sub-Saharan Africa. Yellow fever (*Flaviviridae*) is mainly reported from Africa and South America. Dengue hemorrhagic fever/dengue shock syndrome has a worldwide distribution. Because of the increasing prevalence of international travels, however, infected individuals may be encountered anywhere on the planet.^{1,2}

In the 10th-century Persian medical texts, there is a description of high fever, myalgia, flushing, eye redness, confusion, and epistaxis that is named *sunakhus* fever and could be an early description of hemorrhagic fever.^{3,4} It is very possible that during the ancient time and middle ages, rodent- and mosquito-borne zoonotic viruses, including those causing hemorrhagic fever, were among the main threats to human society.⁵

HISTORY

World History of Hemorrhagic Fever With Renal Syndrome

Hemorrhagic fever with renal syndrome had been discovered and re-discovered many times in different places.^{5,6} In 1913, an epidemic nephritis reported in East Siberia,⁵ and in 1916, Langdon-Brown described a febrile disease with renal

involvement.⁷ Asian viral hemorrhagic fever was first recognized in 1951 among soldiers of the United Nations in Korea, who presented high fever, low blood pressure, and acute kidney failure, first known as Korean hemorrhagic fever.⁵ The disease was very soon reported from another region, what nowadays known as HFRS. Hemorrhagic fever of Manchuria, hemorrhagic nephros-nephritis in the Soviet Union, and *nephropathia epidemica* in Europe all were diverse nominations for same condition.^{1,2,5} In Asia and Russia, important pathogens for HFRS include Hantaan, Seoul, and Amur-Soochong viruses. In Europe, Puumala, Dobrava-Belgrade, Saaremaa, and Tula viruses are the main pathogens.¹

Contemporary History of Hemorrhagic Fever With Renal Syndrome in Iran

An early description of an infection with hemorrhagic picture was done by Dr Amin-ol Ashrafi from Tabriz University in 1966 (Figures 1 and 2). He precisely described a group of patients from Sarab region of the East Azarbayejan who presented with fever, myalgia, headache, flushing, palpable purpura, epistaxis, and gastrointestinal

and vaginal bleeding. He also noted the worsening of kidney function in a group of these patients. Preliminary laboratory study of these patients revealed leukocytosis and thrombocytopenia. He did not perform any serologic study, but because of seasonal characteristic of this disease, appearing during spring and summer, he speculated that it would be an “Asian epidemic hemorrhagic fever,” nowadays named hantavirus HFRS.⁸ He continued his interest and observed and managed more than 40 similar cases during the next coming 4 years and published another article detailing cases and named his newly described disease as “viral hemorrhagic fever of Sarab.^{8,9}” The mysterious disease was known to local people for many years, and was called *hasbeh ghramikh*. Amin-ol Ashrafi collected 24 serum samples from the patients (Figure 2). During the second sample collection in September 1969, 5 blood samples were collected from the patients in their coalescence period and 160 from healthy individuals in the same endemic area. All samples were kept at -20°C and sent to virology section of the Health Research Institute in Tehran to be examined for a panel of antibodies



Figure 1. Professor Amin –Ol Ashrafi (3rd person standing from the right) and his colleagues at the Faculty of Medicine, Tabriz University, in 1962 (courtesy of Museum of Tabriz University of Medical Sciences).

Sommaire des Articles.

I- Observations et rapport (pour la première fois) sur une épidémie bénigne d'une sorte de Fièvre Hémorragique en extension dans l'Azarbaïdjan de l'Est.

« Des travaux cliniques du Service Médical de l'Hôpital Universitaire Pahlavi de Tabriz »

Dans cet article les auteurs commencent par exposer leurs observations sur une sorte de Fièvre Hémorragique que s'était déclarée, sous une forme épidémique à SARAB, ALANBRAGOOCH, MEHRAVAN et dans quelques districts de l'Azarbaïdjan de l'Est.

Il est probable que cette maladie est la Fièvre Hémorragique qui a récemment sévi aux Philippines, en Thaïlande, à Bangkok, à Manille, à Singapour, en Corée et dans le bassin de la Volga. L'Organisation Mondiale de la Santé a suivi de près l'évolution de cette épidémie et a essayé de trouver des moyens efficaces pour l'empêcher de s'étendre.

Pour éclairer les lecteurs, les auteurs citent les deux groupes distincts de cette Fièvre Hémorragique au point de vue d'épidémiologie, pathologie, et de manifestations cliniques. Le premier groupe comprend les Fièvres Hémorragiques relatives au Dengue, dont les régions d'extension dans le monde sont les Philippines, Bangkok, Thaïland, Singapour etc.

L'agent pathogène principal de ce groupe est connu au nom de Virus CHIGANGUNYA, le vecteur est STEGOMIYA-AEDES AEGYPTI (genre de Culicidae) qui se multiplie près des maisons et qui transmet la Fièvre Jaune et Dengue. Le réservoir en étant les rats, les lièvres et les autres rongeurs sauvages.

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گزارش (برای اولین بار)

مشاهده یک همه‌گیری کوچک تب هموراژیک اپیدمیکی

و ویروسی همراه با چند مورد مرگ در یک منطقه از آذربایجان شرقی ایران

و ازبادهای مطالعات بالینی بخش داخلی بیمارستان بهلوی دانشکده پزشکی تبریز

از مدت سه سال قبل در بین بیمارستان‌رپائی و بستری بخش داخلی بیمارستان بهلوی

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Figure 2. First pages of the first report of professor Amin-ol Ashrafi (abstract in French) who described the first 9 patients with hemorrhagic syndrome in Iran, published in December 1966 issue of the Medical Faculty and Pharmacology Journal of Tabriz University (courtesy of the Medical Journal of Tabriz University of Medical Sciences).

against some newly discovered arborviruses at that time. Interestingly, in the first collected batches, 13 of 24 patients (54%) were positive for West Nile virus, 4 (16.5%) for Dengue fever, 7 (29%) for Russian summer encephalitis virus, and 14 (58%) for chikungunya virus. Some samples had positive results for more than one virus. The positive rates in the control group were 32.5%, 8%, 5.5%, and 26%, respectively. In the second collected samples, all five samples were positive for chikungunya virus, 4 of which were also positive for West Nile virus and 3 had additional positive serologic results for Russian summer encephalitis virus. Dengue fever serology was detected in one of them. Although there are cross-reactivity between different hemorrhagic fever viruses, as he showed, diverse viral etiologies may be involved.

In his 80-page length article that was published in May 1969, Amin-ol Ashrafi has described in detail all his 40 patients. His report was the earliest and greatest observation of hemorrhagic fever

in Iran during the 20th century and his genuine reports could be the first descriptions of west Nile encephalitis virus infection, Dengue fever, and hemorrhagic fever with renal syndrome in Iran.^{8,9}

In 1969, Dr Valiollah Asefi from the Faculty of Health of Tehran University, who had collaboration with Dr Amin-ol Ashrafi, reported a group of patients from a rural area of Khalkhal near the city of Ardabil in Azarbayejan province. They presented with quite the same symptoms and signs as had been described by Amin-ol Ashrafi and mainly presented during spring and summer.⁹ He considered the possibility of Crimean hemorrhagic fever for some of his patients.¹¹ Asefi also considered the possibility of other infectious diseases such as yellow fever, non-icteric leptospirosis, typhus fevers, and also Moschowitz disease (thrombotic thrombopenic purpura) or Henoch-Schonlein purpura, but his main consideration was arboviruses infection.¹⁰ The works of these two pioneers were a pivotal base for studies in this field in future years to come.

OTHER VIRAL HEMORRHAGIC FEVERS

The presence of Crimean-Congo hemorrhagic fever virus in Iran was first identified in studies of livestock by Chumakov in the 1970s.¹² In 1999, there was an epidemic in Iran that reached its peak of incidence in 2002. After that different clinical reports came from different parts of Iran.^{11,12} Chikungunya disease is characterized by fever, headache, myalgia, rash, and arthralgia. In 1969, Amin-ol Ashrafi finally concluded that his mysterious disease was arbovirus-related hemorrhagic fever and most probably chikungunya, although he did not confirm this special diagnosis definitively.^{9,14} We did not find any documented report of this disease later in Iran. Dengue viruses belong to the family of *Flaviviridae*. Dengue virus produces a range of mild disease to the dengue hemorrhagic fever/dengue shock syndrome. It is characterized by abrupt onset of fever and myalgia. Thrombocytopenia, hemorrhagic manifestation, and leakage-induced hemoconcentration are usually detectable before the onset of shock.¹⁴ Many of Amin-ol Ashrafi's patients had the same presentation and he also found positive serology for dengue virus among his patients.⁹ In a recent report by Chinikar and colleagues from Iran, 15 serum samples from a total number of 300 Iranian patients who tested negative for Crimean-Congo hemorrhagic fever (5%) were positive for anti-dengue virus immunoglobulin G.¹⁵

West Nile virus is a common cause of febrile disease with or without central nervous system involvement in Africa, the Middle East, southern Europe, and Asia.^{1,2} In Amin-ol Ashrafi's report, there were positive tests for West Nile virus. In a recent report by Chinikar and colleagues, 300 human blood samples and 315 equine blood samples from different geographic zones of Iran were tested for anti-West Nile virus immunoglobulin G antibody.¹⁶ The results were positive in 4 (1.3%) of human and 9 (2.8%) of equines samples. In another report, 5% of blood samples among 500 blood donors were positive for anti-West Nile virus antibody.¹⁷ Recently, we found a positive serology for West Nile virus in a patient with fatal hemorrhagic fever (MA and SC).

CONCLUSIONS

Renal involvement does not restrict to a specific hemorrhagic fever family. The most important

concern is public awareness and providing information about the disease and their routes of transmissions.

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CONFLICT OF INTEREST

None declared.

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