

# Epidemic Hemorrhagic Fever in Korea

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Korean Hemorrhagic Fever was recognized during the Korean War(1950-1953) and intensive studies have been done especially in early 1950's. However, the etiologic agent, vector, and reservoir are not known conclusively. The occurrence has two peak seasons in spring and autumn, and is not limited to military personnel in front lines but also civilians are attacked. Still the study is going on.

**Key Words:** Epidemic Hemorrhagic fever.

In the spring of 1951, during the Korean War (1950-1953), the United Nations troops encountered a new acute, self-limited, infectious disease of unknown etiology characterized by fever, prostration, anorexia, vomiting, abdominal pain, proteinuria, renal failure, toxemia, and hemorrhagic manifestations.

The available evidence such as clinical course, laboratory data and autopsy findings indicates that it is a disease apparently similar to a clinical entity designated as Epidemic Hemorrhagic Fever (EHF) in Manchuria by the Medical Department of the Japanese Army or Hemorrhagic Nephrosonephritis in far eastern Russia by Russian workers. Many writers have quoted one article written by a Russian author in 1944 and another by a Japanese author in that same year. However, no English editions of either of these articles is available to us at the present time.

Review of its epidemicity and pathogenesis suggest the possibility of its presence in Korea before 1950, although it was not reported. It may have been missed mainly because of lack of knowledge and interest on the part of the physi-

cians and because of its rare occurrence in a special ecology<sup>1)</sup>

## HISTORY OF STUDIES ON KOREAN HEMORRHAGIC FEVER (KHF)

Rarely has an infectious disease been investigated as intensively as was Korean Hemorrhagic Fever (KHF) from 1951 to 1954.<sup>2)</sup> In spite of the efforts made nationally and internationally, the etiologic agent is yet to be found. And the pathogenesis, mode of transmission and mechanisms of the disease are still unclear.<sup>3)</sup>

In December of 1951, a symposium on epidemic hemorrhagic fever was held in Korea at the Far East Command Conference on EHF and this discussion was dealt with in the *Annals of Internal Medicine*.<sup>4-10)</sup> In April of 1953, The 38th Parallel American-Korean Medical Society dealt with EHF in their symposium and this was published in the *American Journal of Medicine*.<sup>11-22)</sup> In both conferences, epidemiologic and clinical experiences were reviewed by the medical officers who observed during the war in Korea. Some other clinical case analyses were reported. 3,23,24,25,26,27)

Several reports of cases appearing in the U.S. came out, reports of soldiers becoming ill 30 days after returning from military service in Korea.<sup>28,29,30)</sup>

In addition, several epidemiological studies were done by military medical officers<sup>31,32)</sup> and other researchers working in the civilian farm population.<sup>33)</sup>

Some studies of vectors and/or reservoirs were done also and an arthropod was suggested to be a possible vector of Korean Hemorrhagic Fever.<sup>34)</sup> Meanwhile, rodents were assumed to be the reservoir of the infection.<sup>35)</sup>

In 1961, an EHF team was organized in the Korean army as a regular research and treatment unit and to this day this unit is functioning as a Korean Hemorrhagic Fever Research Center in the Capitol Armed Forces General Hospital, which provides free medical care to the Korean military personnel and civilian EHF patients. Numerous epidemiologic and clinical studies have been done by this team and published mainly in the Korean language. A collection of articles on KHF mostly in English as a single volume was published in 1973.<sup>36)</sup>

Some other research efforts have been made by those who are interested in viral studies. Okuno and Kim reported their failure to prove Arenavirus infection among the small mammals from an endemic area of KHF<sup>37)</sup> Also electron microscopic studies on megakaryocytes in KHF were made.<sup>38)</sup>

Recently Lee reported isolation of the etiologic agent of KHF although the report was definitely preliminary.<sup>39)</sup> This report is one of Lee's interim reports. He and his associates are continuing studies.

Still those who are interested in KHF pay attention to this disease because etiology and pathogenesis as well as the vector are not clearly known yet except that arenavirus may be a possible agent and the tick may be a vector.

## EPIDEMIOLOGY

During and just after the Korean war, the disease was confined to the villages near the Chulwon area located at 38 degrees N. parallel, just south of the Demilitarized Zone in an endemic fashion. However, it has gradually spread in a southwesterly direction over the years.<sup>39)</sup> Nowadays KHF patients sometimes occur in the southern part of Korea and several hundred civilian patients have been reported annually since the 1970's. That the disease is spread southward and civilians are attacked is important in controlling the disease as well as in the epidemiological aspect. The first incidence reported in the civilian population was in 1954<sup>33)</sup> and there have been no reports between 1955 and 1963. Since 1964, about 100 to 400 civilian patients have been reported annually.<sup>39)</sup> No civilian was permitted to enter the endemic focus area during the war because of the forward line of the army, however, cultivation of rice paddies was allowed partly in 1954 and this could have provided the chance for civilians to become infected with KHF.

Season: Sporadic cases occur the year around. Nevertheless, the seasonal incidence has two distinct peaks; one in May and June and the other in October and November. They are the dry seasons of the year, when rainfall is light and sporadic. These seasonal incidences coincide with the greatest number of rodents which are presumed to be a vector.

Sex, age and race: In Korea cases occurred predominantly among the soldiers of the front-line troops during the war, but thereafter the disease has occurred with equal frequency in all sensitive age groups of Korean civilians who moved to the endemic area, with a relatively low incidence rate among children and the aged who have less chance of being exposed to the patho-

genic agents.

On the epidemicity among Korean farmers in the endemic area, the disease occurred in men and women alike. There was no racial difference in sensitivity to the disease. Also the morbidity rate did not vary with the specialty, the duty or the environment of the soldiers among the United Nations troops based in the endemic area.<sup>1)</sup> Incidence was thought to be higher among the United Nations troops than in the Korean Army<sup>4)</sup> and it was believed that Koreans were less susceptible to EHF than were those of the United Nations forces.<sup>31)</sup> This difference is thought to be merely an apparent one because the incidence among Korea army personnel may not have been reported well during the war.

**Endemic area:** During the Korean War, the endemic area was near the Demilitarized Zone; however, at present the endemic area which has been extending over the whole of South Korea, is concentrated in the central part of South Korea.<sup>1)</sup> Nowadays, almost all of the cases occur rather sporadically. An outbreak shows a simple curve of incidence without a secondary case.

The occurrence of disease ranges from 100 to 400 cases each year. The incubation period is from 3 to 4 weeks (7 to 35 days). The case fatality rate was previously 3 to 15%, but now it is less than 5 to 7%. If detected early, the fatality rate is rather low. No person-to-person communicability has been observed yet.

## ETIOLOGY AND TRANSMISSION

In spite of intensive research since 1951<sup>26)</sup>, the effort to isolate the causative agent has not yet met with success. ; Although Lee has reported isolation of the etiologic agent from the wild rodent, *Apodemus agarius coriae*, and from the blood of patients with Korean hemorrhagic fever, it is only a preliminary report.<sup>39)</sup>

It has not been proved that arenavirus is transmitted among Korean small field mammals. A hypothesis that Korean hemorrhagic fever is caused by a virus of small field mammal origin has not been proved.<sup>37)</sup>

Regarding the mode of transmission, it is presumed that the etiologic agent probably is a virus carried by blood-sucking arthropods according to epidemiological viewpoints. Korean hemorrhagic fever is similar to the so-called epidemic hemorrhagic fever in Manchuria and far eastern Russia. However, the isolation and culture of its causative agent have not been yet successful and its natural reservoir, vector and transmission route have not been identified. (*Apodemus agarius* has been thought to be a possible reservoir.) Thus it is still a mysterious disease.

## SYMPTOMS

Clinical courses may be divided into five phases.

- 1) Febrile phase : 1 to 2 days. — acute onset, chills, fever (100° to 106°F), headache, back pain, anorexia, nausea, vomiting, mild photophobia, injected pharynx, dizziness, generalized myalgia
- 2) Hypotensive phase : 2 days to one week — shock, hemoconcentration, marked proteinuria (about 5th day), erythema on face and neck, conjunctival injection and edema, diffuse reddening of skin markedly over face and neck to chest and back

- 3) Oliguric phase : 8 to 12 days --- anuria, uremia, increased BUN, afebrile, hyperkalemia, hyperphosphatemia, hypocalcemia, CNS abnormality (convulsion and delirium may ensue), myocarditis, hemorrhage
- 4) Diuretic phase : 2 to 3 weeks -- electrolyte imbalance, acidosis, polyuria, inability to concentrate urine
- 5) Convalescent phase: 3 to 6 weeks -- Symptoms disappear more or less rapidly as do the hemorrhagic phenomena.

Two thirds of the causes of death are uremia and one third, shock.<sup>23)</sup> Uremia may develop independently of hypotension or shock. Hyperkalemia, pulmonary edema and hypervolemia are common.

## DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Diagnosis is mainly based on the symptoms and a history of exposure to the endemic focus area. In Korea, every suspected person, military or civilian, is transferred to the EHF center in Seoul, capitol city, and is observed/treated free of charge.

Usually it is very difficult to diagnose KHF in the febrile phase because the symptoms are not yet specific enough in this early stage. However, physicians have become experienced during their military service and easily diagnose it in the subsequent phases.

Differential diagnosis is between;

epidemic typhus fever	purpura
meningococccemia	hemophilia

bacterial endocarditis	relapsing fever
acute leukemia	leptospirosis
acute glomerulonephritis	drug poisoning

## PATHOLOGY

- acute onset of severe hemorrhagic tendency and acute renal failure
- extensive necrosis of kidney, compression and distortion of the loops of Henle and collecting tubules
- focal necrosis of adrenal gland, diffuse hemorrhagic necrosis in adrenal cortex, a little altered adrenal medulla
- diffuse severe hemorrhage in the right atrium of the heart
- hemorrhage and focal necrosis in the anterior lobe of the pituitary gland
- retroperitoneal hemorrhage
- pulmonary edema
- petechiae and ecchymoses, usually small, in G-I tract, most numerous hemorrhages along the summits of the rugal folds in the body of the stomach

## TREATMENT

Symptomatic and supportive treatment are available. Careful fluid restriction and bed rest as well as sedation are essential. Control of body temperature is necessary and aspirin or cold sponging are recommended for high fever. Anticoagulant treatment is questionable.

## SUMMARY

1. First recognized in spring 1951 during the Korean war (1950-1953) among the United Nations troops in Korea.
2. Intensive studies have been done; still the

etiologic agent, vector, reservoir and pathogenesis are not known conclusively. Recently, isolation of the etiologic agent was reported, although definitely preliminarily.

3. The disease occurred first among military personnel in the front lines near the Demilitarized Zone (38 N. parallel) in the early 1950's. Since the mid 1960's military as well as civilian personnel have been attacked. Patients also are identified sometimes even in the southern part of South Korea.

4. The occurrence has two peak seasons: spring and autumn.

5. No direct person-to-person spread of infection has been observed.

6. Clinical courses are divided into five phases: febrile, hypotensive, oliguric, diuretic and convalescent.

7. Diagnosis is mainly based on symptoms and history of exposure to the endemic area.

8. Treatment is mainly supportive.

9. The fatality rate is less than 5% nowadays. If diagnosis is made earlier, the fatality rate decreases.

10. Since 1961, the KHF Research Center has been operating, for research and treatment.

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