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ETIOLOGICAL RELATION BETWEEN KOREAN HEMORRHAGIC FEVER AND EPIDEMIC HEMORRHAGIC FEVER IN JAPAN

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SUMMARY The first case of epidemic hemorrhagic fever in Japan was seen in Osaka in 1960. The etiologic agent of this disease has not yet been isolated, but a close etiologic relation between Korean hemorrhagic fever and epidemic hemorrhagic fever in Japan has been suspected because of similarities in the clinical and pathological pictures of the two diseases. This relation has now been confirmed serologically by demonstrating specific immunofluorescent antibodies to Korean hemorrhagic fever virus in 19 of 20 sera obtained from subjects 7 to 17 years after an acute attack of epidemic hemorrhagic fever.

INTRODUCTION

Korean hemorrhagic fever (KHF), also called epidemic hemorrhagic fever (EHF), was recognized for the first time in Korea in 1951. It became a serious problem among U.N. forces during the Korean War (Smadel, 1953; Earle, 1954) and has recently spread all over South Korea.

Diseases that appear to be very similar to KHF are known as hemorrhagic nephrosonephritis or hemorrhagic fever with renal syndrome in Russia (Smorodintsev et al.,

1944 and 1959), as epidemic hemorrhagic fever in China (Ishii, 1942; Kasahara and Kitano, 1943; Kitano, 1944), as nephropathia epidemica (NE) in Scandinavia (Myhrman, 1951; Lähdevirta, 1971), as epidemic nephritis (Gajdusek, 1962) or hemorrhagic fever (Gaon et al., 1968) in Eastern Europe and recently as epidemic hemorrhagic fever in Japan (Tamura, 1964).

Very recently the etiologic agent of KHF was isolated by Lee et al. (Lee and Lee, 1976; Lee and Lee 1978; Lee et al., 1978) and found to be a virus carried by the rodent *Apodemus agrarius coreae*. Diagnostic increase in specific immunofluorescent antibodies to KHF virus was demonstrated by the method of Lee and Lee (1976) in patients suspected of having KHF. By the same technique KHF-related

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illness has also been diagnosed in Russia (Lee et al., 1978), Finland (Lee et al., 1979) and Sweden (Svedmyr et al., 1979).

Epidemic hemorrhagic fever (EHF) was reported for the first time in Japan by Tamura (1964). The causative agent has not yet been isolated, but the idea that there is a close etiological relation between KHF and EHF in Japan was strongly supported by detailed comparison of the two conditions by Tamura (1964).

Serologic evidence for this relation has so far been lacking. Here we report a positive antigenic relation between KHF and EHF in Japan found by the method of Lee and Lee (1976).

MATERIALS AND METHODS

1. Sera

Twenty convalescent sera from 20 suspected cases of typical EHF, seen in Osaka, Japan, between 1960–1970, and specimens from 6 persons with a variety of other known disease (1 systemic lupus erythematosus, 1 pulmonary tuberculosis, 2 bronchial asthma, 1 Behçet disease and 1 cardiac infarction) and from 14 normal subjects were used. The sera were obtained from February through April 1977 from persons recovering from suspected EHF and stored at –20 C until tested. Blind coded sera were mailed from Japan to Korea. Details of the patients and sera are shown in Table 1. A diagnosis of EHF was made on the basis of the clinical picture (Tamura, 1964) and the severity of the disease was assessed from clinical findings and the course of the illness.

TABLE 1. *Immunofluorescent antibody titers against Korean hemorrhagic fever virus in 20 patients with epidemic hemorrhagic fever in Osaka, Japan*

Patient (Sex/Age in year)	Severity of disease	Date of disease year/month/day	Date when serum obtained to test antibody	Years after illness	Antibody titer to KHF virus
M/46	severe	66/06/04	77/02/13	11	16
M/39	mild	66/12/02	77/02/14	11	16
M/43	mild	68/01/15	77/02/13	9	64
F/40	mild	70/02/23	77/02/14	7	128
M/56	moderate	65/11/27	77/02/14	12	16
M/52	severe	64/10/03	77/03/16	13	256
F/23	mild	64/01/16	77/03/19	13	64
M/43	mild	67/11/26	77/03/16	10	128
M/8	severe	66/03/30	77/03/16	11	128
M/33	severe	67/12/12	77/03/19	10	64
M/67	moderate	67/05/21	77/03/19	10	64
M/29	severe	66/04/01	77/03/23	11	8
F/38	mild	60/12/16	77/03/28	17	64
F/37	mild	63/03/18	77/03/28	14	64
M/46	severe	66/11/14	77/03/28	14	64
F/44	severe	66/02/21	77/04/04	11	64
M/16	mild	63/11/17	77/04/04	14	128
F/49	moderate	63/03/25	77/04/04	14	<8
M/30	mild	60/10/03	77/04/13	17	64
M/23	mild	63/03/08	77/04/13	14	32

2. Antigen

The KHF virus, strain 76/118, 12th *Apodemus agrarius jejudoica* passage (Lee et al., 1978), $10^{5.7}$ ID₅₀/0.3 ml in *Apodemus*, was inoculated into normal *Apodemus agrarius jejudoica* intramuscularly, and the infected lung tissues obtained on the 16th day after inoculation were used as antigen.

3. Antibody determination

Immunofluorescent (IF) antibody titrations against KHF virus antigen were done in a blind manner twice in Seoul by the method of Lee and Lee (1976). A final dilution of 1:2,000 Evans blue was inoculated in the solution for staining FITC-conjugated gamma-globulin to human gammaglobulins to obtain better contrast.

RESULTS

Table 1 shows that 19 of the 20 patients suspected to have had EHF 7–17 years previously had antibodies to the KHF virus, while the 6 sera from patients with other diseases and 14 sera from normal subjects living in Osaka had no detectable antibody. The IF antibody titers of the sera from EHF patients ranged from 1/8 to 1/256. IF antibodies to KHF virus have been demonstrated for up to 17 years after illness.

DISCUSSION

We conclude that the syndrome of EHF in Japan is caused by an agent antigenically related, if not identical, to the KHF virus. This conclusion is based on the following findings: 1) tests on sera coded in Japan were repeated twice in a blind manner in Seoul, 2) 19 of the 20 patients suspected of having had EHF had IF antibodies against the virus, 3) none of the 20 control sera contained detectable antibodies, and 4) the proportion of antibody-positive patients among those suspected to have EHF was actually higher than that found by Lee et al., (1978) among mild cases of KHF-like illness in Korea. The mean titers of IF antibodies found in sera of cases of KHF obtained 3 to 14 years after

acute illness (Lee et al., 1978) are almost the same as those in the sera of subjects suspected of having had EHF 7 to 17 years previously.

One antibody-negative case was found among the cases of EHF (Table 1). Although, the donor of this serum had shown typical clinical symptoms of hemorrhagic fever, he had received steroid therapy at an early stage of illness, which presumably explains the negative antibody response against KHF virus.

The sera from M. Tamura M. D. and T. Tamura M. D., which served as part of healthy control sera for the present study, reacted negatively against KHF virus. This is particularly noteworthy considering the fact that they had been in a position to contact closely most of the suspected EHF patients as physicians in charge during whole of the period of prevalence of the disease in Osaka.

With the same technique Lee and Lee (1976) found that KHF-related disease have also been seen in Finland (Lee et al., 1979), Sweden (Svedmyr et al., 1979), and Russia (Lee et al., 1978). However, antisera of Lassa, Machupo, Lymphocytic choriomeningitis, Pichinde and Tacaribe viruses (all of the arena virus group), and of Marburg and Ebola viruses gave negative reactions against KHF virus.

EHF in Japan is clinically milder than KHF, but it is very similar to NE in Scandinavia, as shown in Table 2. Gajdusek (1962) suggested that there is a close etiological relation between KHF and NE and this relation was strongly supported by the detailed comparison of the two diseases by Lähdevirta (1979).

The reservoir of KHF in Korea is *Apodemus agrarius coreae* (Lee et al., 1978) which lives in the fields and mountains, and the reservoirs of hemorrhagic nephroso-nephritis and NE are also suspected to be field mice, since almost all cases of these diseases were farmers and soldiers stationed in rural areas. In contrast, all the cases of EHF reported in Japan (Tamura et al., 1964) were among residents of urban

TABLE 2. *Comparison of clinical features of KHF, NE Scandinavia and EHF Japan*

Symptoms and laboratory findings	KHF	NE Scandinavia ^a	EHF Japan ^b
Acute high fever	100%	100%	100%
Headache	86	common	55
Vertigo	100	common	common
Pharyngeal injection	55	common	40
Cough	40	rare	15
Nausea	82	50	60
Palpable lymph nodes	38	occasional	rare
Petechial exanthema	32	occasional	55
Backache	78	50	common
Proteinuria	96	50	85
Hypostenuria	88	common	common
Polyuria	92	common	common
Hematuria	85	common	10
Oliguria	63	31	common
Anuria	4	rare	rare
Casts	34	frequent	60
Azotemia	94	common	no data
Constipation	60	63	10
Diarrhea	11	rare	35
Enlargement of liver	0	25	20
Enlargement of spleen	7	30	25
Shock	16	occasional	20
Bradycardia	28	occasional	—
Hypotension	80	frequent	—
Hypertension in oliguric state	25	occasional	—
Hemorrhagic manifestations	72	10	50
Increased E.S.R.	72	common	—
Leukocytosis over 10,000/mm ³	91	10	75
Atypical lymphocytes	93	10	80
Thrombocytopenia under 100,000/mm ³	54	—	—
Mild cases	60	50	50
Familial occurrence	0	rare	15

^a Cited from Lähdevirta (1971).^b From clinical records of the donors' sera (M. Tamura, unpublished).

areas of Osaka City during 1960–1972, where there are house rats but no wild *Apodemus* species, and in several families there were 3 or more cases of EHF. It would be a big hazard and a very important problem for residents of urban areas of Japan if the reservoir of EHF

in Japan is actually rats, which live in or near residential areas of large cities.

Finally, it should be noted that a disease which appears to be very similar clinically to KHF, NE and EHF has been reported in several countries in Eastern Europe.

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