Clinical Characteristics of Hantavirus Infections on the Eurasian Continent

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1 Hantavirus Disease on the Eurasian Continent

In 1933 and 1934 two Swedish physicians, working in northern Sweden independently of each other, observed a previously undescribed disease (MYHRMAN 1934; ZETTERHOLM 1934). It was characterized by a rapid onset of high fever, malaise, chills, headache, abdominal, back and often generalized pain, and a renal syndrome with proteinuria and oliguria followed by a diuretic phase. A spontaneous recovery followed all cases described. In 1945 Myhrman proposed nephropathia epidemica

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(NE) as the name for this disease. During the subsequent decades, a large number of cases of this disease were reported from Scandinavia and Finland (MYHRMAN 1945, 1951; LÄHDEVIRTA 1971).

During the Korean conflict (1951–1954) more than 3,000 United Nation soldiers acquired a severe disease characterized by fever, hemorrhagic manifestations and renal insufficiency (GAJDUSEK 1953, 1962; SMADEL 1953; SHEEDY et al. 1954). This disease, at that time largely unknown to western medicine, was recognized as the Korean hemorrhagic fever (KHF). Mortality rates were high, 5–10%, and mainly due to severe bleeding, shock, and renal failure.

However, evidence of a similar disease in the east was documented as early as 1913 in medical records from Vladivostok (CASALS et al. 1970). Russian and Japanese literature, as reviewed by GAJDUSEK (1953) and SMADEL (1953), also revealed the presence of a similar disease in the southeastern part of Russia and in Manchuria. Chinese authorities reported the existence of a similar disease in inner Mongolia (GAJDUSEK 1962). In the late 1950s, Soviet physicians reported diseases with similar features in European Russia. Identical disease patterns had been observed already in the 1930s under the name of Tula fever. A viral etiology was suggested by experiments from the 1940s in which Soviet and Japanese researchers provoked the disease in humans by parenteral injections of bacteria-free filtrates of body fluids (GAJDUSEK 1962). In 1953 Gajdusek postulated the relationship between Asian and European hemorrhagic fevers.

The emergence of KHF during the Korean War marked the starting point of intense studies in search of a causative agent. Circumstantial evidence pointed towards the role of rodents in the spread of these hemorrhagic fevers (HORTLING 1946; CASALS et al. 1970; LÄHDEVIRTA 1971; NYSTRÖM 1977). An agent that reacted strongly in indirect fluorescent antibody assay (IFA) to antibodies from patients that had acquired KHF was identified in lung sections from *Apodemus agrarius* (field mouse) rodents (LEE and LEE 1976, 1977; LEE et al. 1978), captured in rural endemic areas. The responsible virus, named Hantaan (HTN) after the original site of rodent capture at the Hantaan river in Korea, was isolated and could later be propagated in cell culture (LEE et al. 1978; FRENCH et al. 1981). This greatly simplified serological diagnosis of the disease. Soon thereafter, it was possible to show that sera of NE patients from Sweden and Finland reacted with an identical fluorescence pattern to the KHF antigen (LEE et al. 1979; SVEDMYR et al. 1979). When similar NE antigen preparations derived from Finnish *Chlethrionomys glareolus* (bank vole) were available (BRUMMER-KORVENKONTIO et al. 1980) it was found that a high proportion of NE sera reacted with both agents (SVEDMYR et al. 1980). Serological investigations performed in the former Soviet Union described evidence for the circulation of several distinct viruses responsible for similar diseases (GAVRILOVSKAYA et al. 1981; TKACHENKO et al. 1982). Furthermore, evidence of several serotypes in Europe was put forward the same year (LEE et al. 1982b). The NE-causing virus was isolated from lungs of *C. glareolus* adapted to growth in cell culture and named Puumala virus (PUU) after the original site of rodent capture (BRUMMER-KORVENKONTIO et al. 1982). Similar viruses have been isolated from *C. glareolus* and humans in Sweden (JUTO et al. 1997; NIKLASSON and LEDUC 1984; YANAGIHARA et al. 1984).

A virus with immunological properties similar but distinct from HTN was isolated from *Rattus* in urban areas and has become known as the Seoul virus (SEO; LEE et al. 1982a). This virus has been shown to be pathogenic to man and represents a serotype of its own (CHU et al. 1994; LI et al. 1995). Antibodies directed towards this hantavirus have been detected throughout the world possibly due to the wide distribution of its *Rattus* host (LEDUC et al. 1986; CHILDS et al. 1988).

Infections caused by these viruses are major health problems on the Eurasian continent and cause disease in several hundred people annually. The name hemorrhagic fever with renal syndrome (HFRS) was recommended for the diseases within this group, and hantavirus became the accepted term for the causative viruses (WHO 1983; SCHMALJOHN et al. 1985). HFRS is now reported from all over the Eurasian continent. The major hantaviruses associated with HFRS and their main geographical distributions are summarized in Table 1. HTN and SEO virus have been found to cause a majority of the abundance of HFRS cases throughout the eastern part of the Eurasian continent (LEE et al. 1990). Human infection in the west has been reported to be caused by a number of hantaviruses. Lately not only PUU but also the recently discovered Dobrava virus (DOB) has conclusively (by reverse transcription-polymerase chain reaction, neutralization tests, or both) been shown to cause disease in Eurasia (AVŠIC-ZUPANC et al. 1992; HÖRLING et al. 1995; ANTONIADIS et al. 1996; LUNDKVIST et al. 1997b; PLYUSNIN et al. 1997; PAPA et al. 1998). PUU has been found to be the cause of HFRS all throughout Europe with high incidence in European Russia, Finland, and Northern Scandinavia. DOB has (in parallel with PUU) been shown to cause a large number of cases of severe disease on the Balkan Peninsula where this virus was originally isolated (AVŠIC-ZUPANC et al. 1992, 1999; ANTONIADIS et al. 1996; LUNDKVIST et al. 1997b). There are also sporadic cases reported from Central Europe of DOB-caused disease (LUNDKVIST et al. 1997a, 1998; MEISEL et al. 1998). Reports on HFRS caused by SEO- and HTN-like viruses also exist (AVŠIC-ZUPANC et al. 1994; CLEMENT et al. 1994b; ALEXEYEV et al. 1996). Whether these infections were caused by the postulated viruses or the antigenically and relatively closely related DOB awaits further investigation. The PUU-like Tula virus, found in central Europe, has also been associated with sporadic cases of HFRS (VAPALAHTI et al. 1996).

Before 1993, the common belief was that the American continent was free of human pathogenic hantaviruses except for cases of disease related to SEO harbored by rats in major ports. In 1993, an outbreak of a febrile pulmonary syndrome caused by hantavirus, and later named hantavirus pulmonary syndrome (HPS), changed this notion (NICHOL et al. 1993). At first this disease entity seemed

Table 1. Hantaviruses occurring in Europe and Asia presently known to cause disease in humans

Hantavirus serotype	Main rodent reservoir	Human disease	Main geographical distribution
Hantaan	*Apodemus agrarius*	HFRS (KHF)	East Asia
Seoul	*Rattus* spp.	HFRS (Urban)	Worldwide
Dobrava	*Apodemus flavicollis*	HFRS (KHF-like)	The Balkan region
Puumala	*Clethrionomys glareolus*	HFRS (NE)	Europe

unrelated to HFRS, but as comparisons between the two entities presented in this article show, a number of common features are evident.

2 Hemorrhagic Fever with Renal Syndrome: Clinical Aspects

As indicated by the name, the different forms of HFRS are febrile illnesses that generally include various degrees of hemostatic and renal disturbances. The clinical severity of HFRS ranges from asymptomatic infection to fulminant hemorrhagic shock and death. HTN and DOB virus are the causative agents of an illness with considerable mortality, whereas diseases caused by SEO and PUU viruses are less severe. However, the differences in clinical severity within illnesses caused by one virus serotype may be just as great as between the different serotypes. The cause of this variation is unknown. It may involve the virulence of individual viral strains, the infective dose, or host factors.

In typical cases of HFRS, five different phases are recognized (Sheedy et al. 1954). The disease usually begins abruptly with a flu-like, febrile phase. This is followed by a hypotensive phase, often associated with hemostatic disturbances ranging from petechiae and epistaxis to fatal intracranial hemorrhages. Renal impairment ensues, frequently accompanied by marked abdominal and/or back pain. First there is an oliguric phase, with declining urinary output and sometimes anuria, which is followed by a polyuric phase. Finally, there is a recovery phase that may be prolonged over weeks or months. In individual cases of HFRS, not all of these phases are always apparent and they may overlap considerably.

A hallmark of HFRS is vascular dysfunction, including vasodilatation and increased capillary permeability. Vascular dysfunction may explain many of the characteristic features of HFRS, such as hypotension, interstitial edema, and body cavity effusions and it may be of fundamental pathophysiological importance. The mechanisms by which hantaviruses initiate those vascular changes are, however, largely unknown.

2.1 Korean Hemorrhagic Fever

KHF, also known as epidemic hemorrhagic fever and hemorrhagic nephrosonephritis, is a severe form of HFRS. Each year between 50,000 and 100,000 patients are hospitalized in China alone (Lee et al. 1976, 1977; Chen et al. 1986), of which thousands are fatal infections. The more recently isolated Dobrava virus is the cause of a disease that does not seem to differ decisively from KHF (Antoniadis et al. 1987; Avšic-Zupanc et al. 1992, 1999). In the following text, illnesses caused by these two viruses will be referred to as KHF.

As previously indicated, five different phases of the disease are recognized (Sheedy et al. 1954): (1) febrile, (2) hypotensive, (3) oliguric, (4) polyuric, and

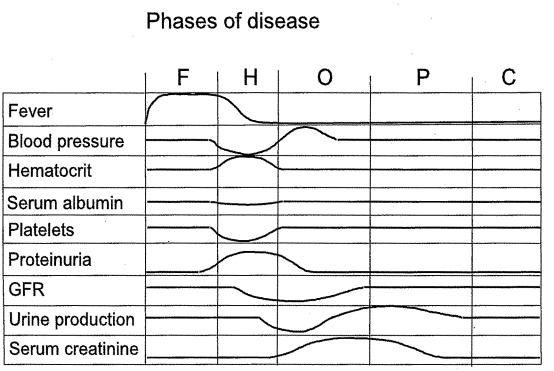

Fig. 1. HFRS, phases of disease. *F* Febrile, *H* Hypotensive, *O* Oliguric, *P* Polyuric, *C* Convalescence

(5) convalescent. Characteristic clinical and laboratory findings of different phases of the disease are summarized in Fig. 1. After an incubation period that may vary from 1 to 8 weeks, there is a sudden onset of high fever and chills (GILES et al. 1954; POWELL 1954; GAJDUSEK 1982; LEE 1989). High fever usually persists for more than 5 or 6 days and is accompanied by headache, myalgia, and nausea. Blurred vision is a typical complaint. Flushing of the face, an erythematosus rash, and conjunctival injections are characteristic clinical findings. Abdominal pain, back pain, or both ensure. At the end of the febrile period, the blood pressure declines and shock may occur. Increased capillary permeability is suggested by the coincidental appearance of hemoconcentration with normal to low serum protein concentrations and with edema, often located to the retroperitoneum. Thrombocytopenia is another characteristic finding and may contribute to the gradually appearing bleeding manifestations (e.g., petechiae of the skin and mucosa, epistaxis, and in severe cases, gastrointestinal or intracranial bleeding). In severe cases, prominent increase of white blood cell (WBC) numbers is observed, including activated lymphocytes and immature granulocytes. In the febrile phase, hematuria and proteinuria appear as the first signs of renal involvement, whereas glomerular filtration rate is essentially unaffected (FROEB et al. 1954). Generally, oliguria or anuria and rising concentrations of serum creatinine ensue, suggestive of a prominent renal involvement. Weight gain and rise of blood pressure, sometimes to hypertensive levels, follow. Polyuria heralds recovery. Diuresis, partly due to impaired tubular function, may be profound, and electrolyte imbalance may occur. The convalescence phase, finally, may be prolonged over weeks or months with a gradual recovery of renal function.

It should be remarked that the clinical expression of KHF varies considerably, and that only about one fifth of the patients develop severe hypotension and hemorrhages (LEE 1989).

2.1.1 Histopathological Findings

Lacking suitable animal models, much of the present knowledge on pathophysiology has been gained by autopsy and histopathological studies. The findings have varied according to the phase of disease investigated.

In autopsies of KHF patients, vascular abnormalities have been generally found, including vascular congestion, extravasation of red blood cells, and perivascular edema (Lukes 1954). In one study, degenerative changes of endothelial cells and of the basement membrane were demonstrated by use of electron microscopy (Li et al. 1984). In patients dying in the early, hypotensive phase of disease, retroperitoneal edema and effusions of the body cavities were observed (Lukes 1954). A typical triad of interstitial hemorrhage involved the right atrium, the anterior pituitary gland, and the renal medulla. Signs of vasculitis were virtually absent.

2.1.2 Renal Findings

On gross examination of fatal cases of KHF, the kidneys were enlarged with a pale cortex and a congested, hemorrhagic medulla. Also, by microscopic examination, the medullary region disclosed the most prominent changes, including congested peritubular capillaries, interstitial hemorrhages, mononuclear cell infiltrates, and interstitial edema. The tubular epithelium showed varying grades of degeneration, from flattening to necrosis. Some glomeruli showed capillary engorgement and focal thickening of the basement membrane (Powell 1954).

2.1.3 Pulmonary Findings

In 4 of 11 patients dying within the first week after onset of KHF, autopsies showed pulmonary edema. This was also a striking finding in 16 of 28 patients dying at later (oliguric and polyuric) stages (Lukes 1954). Pleural effusions were described mainly in the hypotensive phase. At an early stage, edema was held to be associated with vascular leakage, whereas later in the acute phase of the disease, plasma volume overload due to renal failure and resorption of extra-vascular fluids may have contributed to edema formation (Giles et al. 1954; Lukes 1954). On microscopic examination, vascular dilatation and engorgement were universal findings and many of the alveoli were filled with eosin-stained exudate (Powell 1954).

2.2 Urban HFRS

Like the rodent reservoir of SEO virus, *Rattus* species, the associated disease has a worldwide and mainly urban distribution (Lee et al. 1990). As compared with KHF, the illness caused by SEO virus has the characteristics of HFRS but is less severe with a mortality rate of approximately 1% (Table 2) (Lee 1989; Kim et al. 1995). Macroscopic hemorrhagic manifestations are rare. It is associated with more hepatic involvement than seen in KHF. Pulmonary effusions and dyspnea has been reported in SEO hantavirus-infected patients in North America (Glass et al. 1994).

2.3 Nephropathia Epidemica

NE is most prevalent in the European and central parts of Russia, Finland, and Scandinavia. NE is also frequently reported in other parts of Europe.

Table 2. Some clinical and laboratory findings (%) in illnesses caused by Eurasian hantaviruses

	KHF[a]	Urban HFRS[b]	NE[c]
Fever	100	100	98–100
Systolic hypotension (< 90mmHg)	28–80	22	1–16
Pulmonary radiography pathology	13	nd	23–53
Internal hemorrhage	34	5	0–2
Thrombocytopenia ($< 100 \times 10^9$/liter)	78	70	20–52
Hematuria	85	73	56–85
Proteinuria	100	100	94–100
Oliguria (< 500ml/d)	60–65	37	54–70
Dialysis	40	20	0–6

Data are approximated from references:
[a] KHF: LEE 1989, 1991; POWELL 1954;
[b] Urban HFRS: LEE 1989;
[c] NE: KANERVA et al. 1996; LINDERHOLM et al. 1992; LÄHDEVIRTA 1971; MUSTONEN et al. 1994a; SETTERGREN et al. 1989.

Compared to KHF, NE is generally a milder form of HFRS (Table 2). Yet the clinical description of KHF is applicable. Like KHF, NE begins with a sudden onset of fever, chills, nausea, and headache (LÄHDEVIRTA 1971; SETTERGREN et al. 1989). Frequently, abdominal and back pains ensue and may be severe. Hypotension is reported in up to 40% of the patients (LÄHDEVIRTA 1971) but is generally mild. Elevated WBC counts occur in NE, although not to the same magnitude as in KHF. Fatal cases of NE have been associated with marked leukocytosis and shock (LINDERHOLM et al. 1991; VALTONEN et al. 1995). In the early phase of disease, thrombocytopenia is noticed in a majority of the patients (LÄHDEVIRTA 1971). In a prospective study, bleeding manifestations and mild respiratory symptoms were reported in about one third of the patients (SETTERGREN et al. 1989).

Beginning in the late febrile phase, urinalysis discloses proteinuria and hematuria in almost 100% of cases. Renal impairment follows, as indicated by oliguria and rising serum concentrations of creatinine and urea (LÄHDEVIRTA 1971; SETTERGREN et al. 1989; MUSTONEN et al. 1994a). Severe hypertension, blood volume overload, or life-threatening electrolyte imbalance are rare events and dialysis is needed in a minority of patients only. It should be noted that NE does not always proceed with apparent renal affection (ALEXEYEV et al. 1993). In studies of serologically verified cases, no or minimally increased serum creatinine levels were reported in 3/74 (4%; SETTERGREN et al. 1989) and 8/126 (6%; MUSTONEN et al. 1994a) of hospitalized patients, respectively. Thus, a normal concentration of serum creatinine does not exclude a diagnosis of NE.

2.3.1 Histopathological Findings

Only rare fatal cases of NE have been reported. In these instances, renal autopsy findings have been consistent with those of KHF (LINDERHOLM et al. 1991; FORSLUND et al. 1992; VALTONEN et al. 1995). There are, however, several studies of renal biopsy findings in NE. Here, changes within the medulla were most

prominent and, as in KHF, included degeneration of tubular epithelial cells and interstitial edema with infiltration of red blood cells and leukocytes (LÄHDEVIRTA 1971). In a recent study of serologically verified cases of NE, the most common finding was an acute tubulointerstitial nephritis, whereas glomerular changes were reported in only 25% (MUSTONEN et al. 1994b).

3 Similarities Between HFRS and HPS

In 1993, a novel hantavirus infection was recognized in the United States. The clinical picture differed from HFRS and the syndrome was to be named HPS. The mortality rate was as high as 50%. The main difference from HFRS was the occurrence of a severe non-cardiogenic pulmonary edema early in the course of disease and less-severe renal complications.

It may seem surprising that hantaviruses causing HFRS and HPS are closely related, yet have so different clinical expressions, i.e., the predilection for renal and pulmonary involvement in HFRS and HPS, respectively. For example, Sin Nombre virus, associated with the highly lethal HPS, is serologically and genetically more closely related to Puumala virus, which causes a comparably mild disease, than to Hantaan virus, the etiological agent of the more severe form of HFRS.

However, the differences in clinical pictures between HFRS and HPS may not be as marked as it seems at first glance. The differences in organ manifestations may reflect only the major localization of injury imposed by similar underlying pathophysiological events. Both diseases are febrile illnesses with an acute onset. In both syndromes, a more generalized vascular involvement (capillary leak and vasodilatation) is apparent as demonstrated by hypotension, hemoconcentration, and vasodilatation. Other laboratory features in common include thrombocytopenia, proteinuria, and leukocytosis, with occurrence of activated lymphocytes in peripheral blood. The main clinical difference between the two conditions seems to be that the mainly afflicted vascular beds differ, in HFRS capillaries of the renal medulla, and in HPS pulmonary capillaries. Nevertheless, many of the basic clinical and laboratory aberrations are shared in the two conditions.

3.1 Renal Manifestations

Renal impairment is typical in HFRS. In addition, in HPS, and in particular HPS associated with Bayou and Black Creek Canal viruses, a modest to prominent renal involvement has been reported (KHAN et al. 1995; HJELLE et al. 1996). Moreover, there are several reports of HFRS cases without apparent renal impairment (SETTERGREN et al. 1989; ALEXEYEV et al. 1993; MUSTONEN et al. 1994a). Thus, the difference in renal dysfunction in HFRS and HPS may not be as clear-cut as generally perceived.

3.2 Pulmonary Manifestations

Non-cardiogenic pulmonary edema is a characteristic trait of HPS. The spectrum of the disease may, however, be wider. Recent reports suggests that HPS, associated with Sin Nombre virus, may proceed without apparent pulmonary symptoms (KITSUTANI et al. 1999; ZAVASKY et al. 1999).

In HFRS, respiratory tract symptoms are not usually included in the general description. Nonetheless, there is evidence of pulmonary involvement in the disease. In the original reports of HFRS in 1954 among 828 patients, pulmonary complications were recorded in 6% (GILES et al. 1954) and fatal pulmonary edema in 2% (LUKES 1954). In these reports, pulmonary complications were, in fact, one of the main causes of death. Among 181 patients subjected to radiological examination, pneumonic infiltrates were found in 3% and congestive changes in 10% (POWELL 1954). These data all involve the Hantaan virus-caused form of HFRS. In spite of this, there have been few studies focusing on the pulmonary aspects of HFRS, possibly because other, more prominent symptoms, e.g., vascular, hemostatic, and renal disturbances, dominate the clinical picture.

More recent studies, however, have shown that pulmonary manifestations can be demonstrated even in mild HFRS. In NE, caused by Puumala virus, pulmonary edema has been reported only rarely (CLEMENT et al. 1994a; KANERVA et al. 1996). Among a variety of general symptoms in the acute phase of NE, cough has been recorded in 6–32% of the cases. (LÄHDEVIRTA 1971; SETTERGREN et al. 1989; MUSTONEN et al. 1994a). In three Scandinavian studies, radiological pulmonary changes were noted in 27/97 (28%), 10/19 (53%), and 13/55 (23%), of the cases (LÄHDEVIRTA 1971; LINDERHOLM et al. 1992; KANERVA et al. 1996). The radiographic changes included interstitial infiltrates in the perihilar tract or the peripheral and/or lower parts of the lungs, as well as pleural effusions. There was an association of radiological findings with the severity of the clinical condition (LÄHDEVIRTA 1971) as well as with parameters of inflammation (LINDERHOLM et al. 1992; KANERVA et al. 1996).

In bronchoalveolar lavage (BAL) fluid of five patients in the acute phase of NE, increased numbers of macrophages, activated macrophages, CD8 T cells, and NK cells were found (LINDERHOLM et al. 1993). Numbers of CD4 T cells and B cells were normal. Similar to HPS (ZAKI et al. 1995), and in contrast to the adult respiratory distress syndrome (ARDS), only a modest accumulation of neutrophils occurs in the lower respiratory tract in the acute phase of NE (LINDERHOLM et al. 1993). The fibronectin concentration in BAL fluid was higher in patients with NE than in a control group. Altogether, a local host response in the lower respiratory tract was found in NE compatible with what might be expected to occur in viral disease. Moreover, the pulmonary changes in NE may be similar by nature to those seen in HPS.

The cardiac and pulmonary functions were investigated in 13 patients in the acute phase of NE (LINDERHOLM et al. 1997). Compared to reference values, the patients showed a decreased diffusion capacity for carbon monoxide and an increased pulmonary clearance of inhaled technetium-99m-labeled diethylenetriamine penta-

acetic acid. In 4/11 patients, arterial hypoxemia was found. The cardiac function was normal. In sum, an alveolocapillary lesion best explained the pulmonary dysfunction.

Altogether, pulmonary changes seem to be far more common in HFRS than is usually recognized. It should be remarked that the illness of patients with HFRS referred to was relatively mild (LÄHDEVIRTA 1971; LINDERHOLM et al. 1992, 1993, 1997; KANERVA et al. 1996). Thus, a pulmonary involvement seems to be a general trait of HFRS and not only an occasional finding in severe cases. Even though the occurrence of pulmonary manifestations in HFRS might seem to reconcile poorly with the relative sparseness of respiratory symptoms, it should be recalled that HFRS is associated with marked general symptoms for which an impaired pulmonary function may be partly responsible.

In summary, HFRS and HPS share many clinical characteristics. In both forms of illness, renal and pulmonary involvement may occur, even if the degree of severity varies. In spite of differences in clinical expression, basic pathogenetic mechanisms may be similar.

4 Prognosis

The overall mortality of KHF is 3–10% (LEE et al. 1990). In a report from the Korean War, the most common causes of death were irreversible shock and pulmonary complications (LUKES 1954). In nonfatal cases full recovery is considered the rule. Severe complications, such as neurological damage and panhypopituitarism may, however, develop because of intracranial hemorrhagic manifestations. Restoration of renal function is generally complete even though this may proceed over months. In SEO or SEO virus-like infections, a relationship between previous and chronic hypertensive end-stage renal disease has been reported in patients from the eastern United States (GLASS et al. 1993). Of patients with end-stage renal disease because of hypertension, 6.5% were SEO virus seropositive.

In NE, there are only occasional reports of fatal outcome (LINDERHOLM et al. 1991; FORSLUND et al. 1992; VALTONEN et al. 1995), and overall mortality rate is $<0.5\%$ (LEE et al. 1990). As in KHF, long-term prognosis seems to be good (LÄHDEVIRTA 1971; SETTERGREN et al. 1989), even if some patients may experience convalescence with fatigue lasting over months. Sequelae due to complications during the acute phase of NE are reported. This includes hemorrhagic complications (ALEXEYEV et al. 1994; SETTERGREN et al. 1983; ZEIER et al. 1992), Guillain-Barré syndrome (ESSELINK et al. 1994; FORSLUND et al. 1992) and other neurological complications (ALEXEYEV et al. 1995), and the development of pituitary insufficiency (FORSLUND et al. 1992; SETTERGREN et al. 1992). Permanent renal injury is probably rare in NE (LÄHDEVIRTA 1971; SETTERGREN et al. 1989). Tubular dysfunction, disclosed as impaired capacity to concentrate the urine, may persist for months. NE followed by hypertension has occasionally been reported (KLEINKNECHT and ROLLIN 1992). A similar investigation on Swedish patients

could not reveal an overrepresentation of seropositivity for hantavirus (PUU virus) in end-stage renal disease (SETTERGREN et al. 1998).

After recovery from HFRS, long-lasting immunity follows and reinfection does not seem to occur (LEE 1982).

5 Diagnosis of HFRS Caused by Hantaviruses in Eurasia

The diagnosis of HFRS had been based on clinical and laboratory findings up until the point when the hantaviruses were found in lung tissue of rodents in various regions of the Eurasian continent (LÄHDEVIRTA 1971; LEE et al. 1976; NYSTRÖM 1977; BRUMMER-KORVENKONTIO et al. 1980; AVŠIC-ZUPANC et al. 1994). Clinical diagnosis is still the most important means of deciding if a patient has HFRS and the incentive for specific diagnostic testing. For specific serodiagnosis, hantavirus-infected lung sections were used as antigen in indirect IFA (LEE et al. 1976; BRUMMER-KORVENKONTIO et al. 1980). When hantavirus could be propagated in cell culture, this was used as antigen in IFA and ELISA (FRENCH et al. 1981; TKACHENKO et al. 1981). Lately, recombinantly produced hantavirus nucleocapsid proteins have been widely used in the enzyme-linked immunosorbent assay (ELISA) format for serological diagnosis of acute hantavirus infections and for epidemiological purposes (ROSSI et al. 1990; KALLIO-KOKKO et al. 1993; ZÖLLER et al. 1993; ELGH et al. 1996, 1997). Sera from hantavirus-infected patients react strongly to these proteins early in the course of disease (ELGH et al. 1997, 1998). A major drawback is the cross-reactivity seen between the different hantavirus serotypes. For serotypic differentiation, neutralization tests remain the most precise serological tool available (LEE et al. 1985; NIKLASSON et al. 1991; HÖRLING et al. 1992; CHU et al. 1994, 1995). An interesting approach for serotyping is under development, using non-cross-reactive parts of recombinantly produced nucleocapsid proteins of hantaviruses (MORII et al. 1998). Polymerase chain reaction specific for hantaviruses has been tried in HFRS but is not sensitive enough to be considered as a routine diagnostic tool (ARTHUR et al. 1992; HÖRLING et al. 1995; ANTONIADIS et al. 1996; PLYUSNIN et al. 1997). Most patients present specific IgM at onset of disease and this type of test in different formats is therefore the method of choice in HFRS diagnostics in endemic areas (ELGH et al. 1995, 1998). Moreover, specific IgA antibodies closely follow the kinetics of IgM and may provide additional diagnostic information (ELGH et al. 1998).

6 Treatment

The treatment of patients with HFRS relies on good supportive care. In severe cases of HFRS, intensive care facilities may have contributed to a reduction in mortality observed over the last decades.

Many drug therapies have been tried in HFRS. One strategy has been to use immunomodulatory drugs. For example, in the early phase of KHF, interferon-α (Gui et al. 1987) and steroids (Qian et al. 1990) were tried without evident effect. Cyclophosphamide, an immunosuppressive alkylating agent, administered early was shown to halt progression to hypotensive and oliguric stages (Dai et al. 1981). The only medication that has shown some promise is the antiviral agent ribavirin, which efficiently inhibits hantavirus growth in vitro (Kirsi et al. 1983). In a randomized study on KHF, ribavirin was reported to significantly reduce mortality when administered early after onset of disease (Huggins et al. 1991). The risk of hemorrhages and of entering the oliguric stage was also reduced in the ribavirin-treated group.

Still, proper supportive care remains fundamental in the treatment of HFRS. In the hypotensive and oliguric phases, fluid restriction is recommended and was in fact a measure reported to reduce the mortality among US soldiers afflicted with KHF (Steer 1955). In cases with severe hypotension, colloidal solutions and vasopressor agents are preferably used to maintain adequate blood pressure. Careful control of electrolyte balance is important. Antipyretic and analgesic agents are frequently needed. Drugs that may interfere with renal function, such as non-steroid anti-inflammatory drugs and renal toxic drugs, should be avoided. In severe forms of HFRS, dialysis may be required, particularly in the oliguric phase if hyperkalemia, severe hypertension, or hypervolemia occur. In NE, dialysis is rarely needed, even in cases with prominent elevation of serum creatinine concentration and profound oliguria (Lähdevirta 1971; Settergren et al. 1989).

7 Strategies for Future Treatment Trials

There are studies suggesting that host inflammatory responses are involved in the pathogenesis of HFRS and HPS. In particular, certain cytokines, such as tumor necrosis factor (TNF)-α, have been associated with hantavirus infection (Linderholm et al. 1996; Temonen et al. 1996; Mori et al. 1999). If cytokines can be shown to be among the determinants of the outcome of hantavirus disease, this should be a clue in the search for treatment of fulminant cases. Potential therapeutic interventions may be tried to down-regulate the inflammatory responses in severe cases of HFRS. Work to find inhibitors of TNF-α is in progress (Knight et al. 1993; Moreira et al. 1993; Evans et al. 1994). As a basis of future trials, it seems worthwhile to assay TNF-α and other cytokines in various forms of HFRS and in HPS.

Based on studies suggesting a favorable effect in KHF of ribavirin (Huggins et al. 1991), a combination of antiviral and immunomodulatory treatment would be particularly interesting. Inhibition of the inflammatory responses might possibly induce an exacerbation of hantavirus replication, an event that would be prevented by concomitant administration of antiviral drugs.

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