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Haemorrhagic fever with renal syndrome in Korean children

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Abstract. Haemorrhagic fever with renal syndrome (HFRS) is an acute disease caused by Hantavirus and clinically characterised by abrupt onset of fever, various haemorrhagic manifestations and transient renal and hepatic dysfunction. We retrospectively reviewed 63 cases of HFRS in children from 13 different hospitals in Korea who presented over a 15-year period. The age of the patients ranged from 7 to 15 years, with a male to female ratio of 8 to 1. Fifty-four (86%) patients were 10 years or older. On admission, 24 (38%) were in the febrile phase and 35 (56%) were in the oliguric phase. Fever (100%), abdominal pain (91%), headache (76%) and vomiting (73%) were the most common symptoms. Backache, subconjunctival haemorrhage and hypertension were also noted in about one-third of patients. Hypotension was documented in only 7 (11%) patients. Leucocytosis ($>10{,}000/mm^3$) and thrombocytopenia ($<150{,}000/mm^3$) were noted in more than two-thirds of patients. Elevated blood urea nitrogen and serum creatinine was observed in 94% by the 7th (median) day of illness. Elevated aspartate aminotransferase and/or alanine aminotransferase were found in more than two-thirds of patients. Renal biopsy was performed in 12 patients and revealed various stages of acute tubular necrosis with occasional interstitial cell infiltration and oedema. Only 2 showed evidence of interstitial haemorrhage. Eleven patients required 1–3 days of dialysis and the remaining patients required only conservative management. Three (5%) patients died of shock, respiratory failure and pulmonary haemorrhage. All other patients recovered without sequelae. Although childhood cases were much less common than adults, clinical and laboratory findings were in general similar between children and adults.

Key words: Haemorrhagic fever with renal syndrome – Korean children

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Introduction

Haemorrhagic fever with renal syndrome (HFRS) was detected for the first time in Korea in 1951 [1] during the Korean war. In 1976, Lee and Lee [2] developed a specific serological test for this disease and Lee et al. [3] later isolated the aetiological agent, known as Hantaan virus, from the lungs and other tissues of infected *Apodemus agrarius* mice. In 1981, the virus was adapted to tissue culture [4].

Hantaan – related agents are widely distributed throughout the world [5]. At least four distinct Hantaan-related viruses (Hantaan and Seoul virus in Asia, Puumala virus in Central and Northern Europe, Prospect Hill virus in the United States) have been isolated, and comprise a new genus *Hantavirus* of the virus family *Bunyaviridae* [6]. Diseases caused by hantaviruses are now collectively referred to as HFRS [7].

HFRS is a disease characterised by fever, capillary dilatation and leakage of blood, leading to haemorrhagic manifestations and in severe cases, shock and renal tubular disease [7–9]. The incubation period has been estimated to be 2–3 weeks [10, 11]. The clinical manifestations of Hantaan viral infection are diverse, and clinical severity varies from subclinical to severe illness [8, 12]. The clinical course of Hantaan viral infection can be divided into five

phases based on clinical data and underlying physiological aberrations: (1) febrile, (2) hypotensive, (3) oliguric, (4) diuretic and polyuric and (5) convalescent [6, 8, 9]. In mild cases, the hypotensive and oliguric phases may not appear, whereas in severe cases several phases may develop simultaneously [13, 14].

HFRS mainly occurs in adults [8, 12]. Since it is rarely reported in children [9, 10, 15], the purpose of this study was to describe the clinical features of HFRS in large group of Korean children who presented with severe disease.

Patients and methods

We retrospectively reviewed the clinical and laboratory data of 63 children with HFRS, from 13 different hospitals in Korea, who presented between January 1978 and June 1993. HFRS was confirmed by the presence of specific serum antibodies to the Hantaan virus (76–118 strain) using an indirect immunofluorescence test in clinically suspected cases. Fourty-seven patients had a fourfold or greater increase in antibody titre and 16 patients (4 patients 1:320; 2 patients 1:640; 10 patients >1:1,280) had a single IgG titre of 1:320 or greater. The test was performed at the Institute for Viral Diseases, Korea University and at the Department of Microbiology, Seoul National University. In clinically severe cases, the diagnosis has been reported to be correct in 94%–98% on clinical grounds only [12, 16]. Although only single antibody titres were available in 16 of our patients, our diagnosis is likely to be correct, since all patients were severe enough to require hospitalisation. Demographic, epidemiological and clinical information was obtained by review of medical records.

Results

The patients, ages ranged from 7 to 15 years, and 54 (85.7%) were 10 years or older. Fifty-six patients were male and 7 female. Thirty-two (51%) cases occurred in November. The peak incidence of disease occurred between November and January (55 patients, 82%), with a secondary peak occurring between May and July (8 patients, 13%).

On admission, 24 (38%) patients presented in the febrile phase, 3 (5%) in the hypotensive phase, 35 (56%) in the oliguric phase and 1 (2%) in the diuretic phase. A febrile phase ranging from 3 to 11 days (median 6 days) was manifested in all patients. A hypotensive phase of 1–2 days' duration was observed in only 7 (11%) patients; oliguria (median 4 days, range 1–11 days) was observed in 41 patients (65%).

Table 1 summarises the common clinical findings. Fever (100%), abdominal pain (91%), headache (76%) and vomiting (73%) were the most common symptoms in children. Sore throat (27%), cough (19%) and diarrhoea (13%) were also not uncommon. Dyspnoea and seizures were noted in 6% of patients. Haemorrhagic manifestations, including subconjunctival haemorrhage and petechiae in the axilla and/or soft palate, were noted in about one-third of patients. Oedema and hypertension were only noted during the oliguric phase and were seen in 24% and 32% of patients, respectively.

Laboratory findings are summarised in Table 2. These observations were made on day 3–12 of illness. Thirty-nine percent of patients had a haemoglobin of 14 g/dl or greater, with a peak level of 19.6 g/dl. Leucocytosis (total white cell count of 10,000/mm^3 or greater) was observed in 71% of patients. While a differential count was performed in only 36 patients, 23 (64%) of these had a left shift (>5% band forms). Thrombocytopenia (<150,000/mm^3) was found in 80% of patients; proteinuria was present in all. Haematuria and pyuria were noted in 42 (67%) and 5 (8%) patients, respectively. Elevated aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) (>30 IU/ml) were noted in more than two-thirds of patients. Elevated blood urea nitrogen (BUN) and serum creatinine were noted in 59 (94%) patients. Median levels of peak BUN and serum creatinine were 83 and 5.7 mg/dl, respectively on the 7th day (median) of illness (range 3–12 days). In the oliguric phase, hyponatraemia and hyperkalaemia were noted in 48% and 22% of patients, respectively.

Renal biopsy was performed in 12 patients in the diuretic phase and indicated various stages of acute tubular necrosis with interstitial oedema and mononuclear infiltrates. Medullary haemorrhage was observed in 2 patients. Eleven (18%) patients required dialysis (8 haemodialysis and 3 peritoneal dialysis) for advanced renal fail-

Table 1. Clinical manifestations in 63 children with haemorrhagic fever with renal syndrome (HFRS)

Manifestations	Frequency (%)	
	Present series (n = 63)	Adults[a] (n = 104)
Constitutional symptoms		
Fever	100	100
Chill	44	96
Backache	35	91
Weaknes	29	92
Myalgia	21	75
Cardiovascular symptoms		
Hypertension	32	63
Flushing	25	91
Oedema	24	40
Hypotension	11	28
Thirst	11	92
Bradycardia	5	73
Gastrointestinal symptoms		
Abdominal pain	91	92
Vomiting	73	82
Nausea	62	91
Anorexia	33	95
Hiccup	8	54
Haemorrhagic manifestations		
Petechiae	38	95
Subconjunctival haemorrhage	35	16
Melena	6	16
Haemoptysis	5	8
Neurological symptoms		
Headache	76	97
Dizziness	21	88
Blurred vision	13	57
Ocular pain	6	32
Photophobia	5	21

[a] From ref [8]

Table 2. Laboratory findings in 63 children with HFRS

Findings	Range (median)	Frequency (%)
Haematological findings		
Haemoglobin (g/dl)	8.7–19.6 (13.4)	
>14 g/dl		39
Leucocytes (/mm³)	3,800–40,400 (13,250)	
>10,000/mm³		71
Platelets (/mm³)	6,000–312,000 (86,000)	
<150,000/mm³		80
< 50,000/mm³		25
Urinary findings		
Proteinuria (+)		100
Haematuria (>5/HPF)		67
Pyuria (>10/HPF)		8
Biochemical findings		
Serum Na (mEq/l)	103–140 (125)	
<130 mEq/l		49
Serum K (mEq/l)	2.2–7.3 (4.3)	
>5 mEq/l		22
BUN (mg/dl)	7–163 (83)	
>20 mg/dl		94
Serum creatinine (mg/dl)	0.5–13.4 (5.3)	
>1.2 mg/dl		94
AST (IU/ml)	10–1,314 (68.5)	
>30 IU/ml		68
ALT (IU/ml)	10–944 (39)	
>30 IU/ml		80
Serum cholesterol	56–216 (118)	
<150 mg/dl		87

HPF, High power field; Na, sodium; K, potassium; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase

ure, volume overload with hyponatraemia and hyperkalaemia. The mortality rate in our series was 5% (3 patients). These patient died during the hypotensive and early oliguric phases due to shock, respiratory failure and pulmonary haemorrhage. The remaining patients recovered without any significant sequelae.

Discussion

HFRS is a dramatic illness characterised by fever, haemorrhagic syndrome and renal involvement. The endemic area includes Korea, Japan, far-eastern Siberia, north and central China, Russia, Scandinavia, Czechoslovakia, Rumania, Bulgaria, Yugoslavia and Greece. The severe form is common in eastern Asia, while the majority of European cases are mild [7, 17]. Other endemic areas include certain regions of North America, Central America, South America, Africa and recently Australia [5, 11, 12, 17]. The recent outbreak of clinical Hantavirus disease in southwestern regions of the United States highlights the importance of Hantavirus infection as a global problem [18].

Males are mainly affected between the 3rd and 6th decades of life. The disease is rarely seen in children under 10 years [10, 12, 15]. In our series only 9 of 63 patients were under 10 years and the youngest was 7 years. Since 1951, 500–900 adults with HFRS have been hospitalised annually in Korea [12]. However, we could collect only 63 paediatric cases over the last 15 years, suggesting that clinically overt HFRS is very rare in childhood. A recent seroepidemiological survey using an enzyme-linked immunosorbent assay in Chorwon, one of the most endemic areas in Korea, revealed that the seroprevalence was 2.1% in children, with all infections being subclinical [19]. This would suggest that in childhood subclinical infections are much more common than clinically overt disease. The increased incidence in males was ascribed to the fact that males have a greater risk of exposure to the infectious agent, which is carried by reservoirs such as *Apodemus agrarius* in Korea, since most field workers are males [14]. This male preponderance was especially prominent in our series. HFRS has been reported all year round, although there appears to be two peak seasons, namely late spring (May to July) and late autumn (October to December) [12]. Our study revealed a similar pattern.

A detailed description of the clinical manifestations in Korean adults with HFRS has recently been reported [8]. The febrile phase typically lasts 3–6 days and is characterised by abrupt onset of high fever, chill and headache, followed by weakness, dizziness, myalgia, backache, anorexia and nausea. Fever characteristically rises rapidly to a high level. In our patients, fever was observed for 3–11 days. Hypotension occurs on approximately the 5th day of illness and usually occurs during the last 24–48 h of the febrile phase. In severe cases, shock is observed and one-third of deaths are due to irreversible shock. In other series that included both children and adults, hypotension was rarely seen in children (8% of infected children) [9, 20]. In our series also, hypotension was documented in only 11% of patients. The oliguric phase occurs on the 6th–8th day of illness during the recovery from the hypotensive phase. In adult series, oliguria was observed in half of the patients and the duration of oliguria typically was 3–5 days [8, 9]. In our series, two-thirds of the children had oliguria with a duration of 1–11 days. This difference may be due to the fact that our patients had more severe disease. Towards the end of the oliguric phase, restlessness, confusion, tremor or convulsions may develop. The diuretic phase begins on the 9th–14th day of illness and lasts for a few days to weeks. The convalescent phase lasts from 3 weeks to 3 months. Other than the hypotensive phase, the progression of phases was similar between children and adults.

Subjective symptoms, such as anorexia, backache, myalgia, weakness, dizziness, blurred vision, thirst and photophobia, were less common in children. Haemorrhagic manifestations may take the form of ecchymoses, epistaxis and infrequently visceral haemorrhage. Although petechiae were noted in about 95% of adults, they were less commonly observed in our series. In contrast, subconjunctival haemorrhage was more common than in the adult series. However, overall the clinical features were similar between children and adults with HFRS. Subconjunctival haemorrhage, abnormal liver function tests and the need for dialysis for acute renal failure were more common in our series than in a recent report of children with nephropathia epidemica (caused by Puumala virus) [21].

Elevated haemoglobin, leucocytosis and thrombocytopenia were reported in 73%–96% of Korean adults with

HFRS [8], but were observed less commonly in our children. Proteinuria, microscopic or gross haematuria and pyuria have been reported in adult patients and were also common in our series. Elevation of serum creatinine and BUN usually begins on the 4th day of illness and they return to normal towards the end of the 2nd week. Acute renal failure was present in 94% of our patients, with peak BUN and serum creatinine occurring on the 7th (median) day of illness. Increased levels of transaminase and lactate dehydrogenase are common during the first 2 weeks of illness, and approximately 80% of our patients had transient elevations of AST and/or ALT.

The diagnosis is based on clinical manifestations, epidemiological data and the appearance of specific antibodies to hantaviruses in the serum. In atypical cases, such as milder cases without hypotension and oliguria, the indirect immunofluorescence test will establish the diagnosis [12, 17]. The cardinal pathological findings consist of variable tubular epithelial necrosis, marked congestion and medullary haemorrhage of the kidney, selective haemorrhage of the right atrium and necrosis of the anterior lobe of the pituitary gland [22, 23]. Medullary haemorrhage was present in 2 of the 12 patients who had a biopsy. This may be because all of the biopsies were performed in the diuretic phase when the platelet count had normalised. Although recently mesangial cell proliferation has been reported, it was not observed in our patients [24].

Specific therapy has not yet been determined. Recently, in addition to supportive measures, the potential benefit of intravenous ribavirin for the treatment of HFRS was reported [25, 26]. None of our patients received ribavirin; 11 (18%) of our patients required dialysis for volume overload, hyperkalaemia and advanced acute renal failure. Although peritoneal dialysis was performed in 3 of the 8 patients who needed dialysis, haemodialysis seems to be the preferred mode of dialysis for HFRS, since most patients have severe gastrointestinal symptoms.

In the 1960s, the overall mortality rate was reported to be 7%–15%. Recently, there has been a decrease in the mortality rate to less than 5%. This decline has been attributed to early diagnosis and improvement in intensive care measures [8, 27]. The causes of death in patients with HFRS include primary shock, secondary systemic infections, encephalopathy, pulmonary oedema and gastrointestinal bleeding [8, 13, 28]. Most patients recover without residual complications. Permanent neurological sequelae as a result of cerebral haemorrhage or vascular insufficiency and hypopituitarism have been reported on rare occasions [7, 29], but were not observed in our series. In summary, HFRS is rare in children, even in highly endemic areas like Korea. Although there were some differences in subjective complaints in the paediatric patients, overall the clinical features in children were similar to adults.

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Ask the expert*

What are the clinical uses of insulin-like growth factor-I in acute and chronic renal failure?

Key words: Insulin-like growth factor-I – Clinical uses – Renal failure

At present there are no established clinical uses for insulin-like growth factor-I (IGF-I) in acute and chronic renal failure. However, based upon experimental observations, the potential exists for the use of this growth-promoting agent in both settings. We [1, 2] and others [3] have shown that IGF-I administered pre [2] or post acute ischemic injury to rats [1–3] accelerates the recovery of normal renal function and the regeneration of damaged proximal tubular epithelium, and reduces mortality compared with vehicle. Several explanations for the effectiveness of IGF-I in rats have been proposed. First, IGF-I increases the glomerular filtration rate in normal rats and in rats post ischemic injury. Enhancement of glomerular filtration could alter the course of acute renal failure by limiting the extent of injury due to obstruction of tubules by cellular debris. Second, IGF-I is a renotropic agent for the proximal tubule. It enhances DNA synthesis in renal cortex post ischemic injury. Third, IGF-I is an anabolic agent. It reduces protein breakdown and exerts a generalized anabolic action that results in attenuation of weight loss in the setting of the catabolism that accompanies acute ischemic injury. Whatever the mechanism of its action may be, a potential for the clinical use of IGF-I, a growth factor that can be safely administered to humans [4], as a therapeutic modality in established acute tubular necrosis is clearly established. Furthermore, the potential exists for the use of IGF-I as a prophylactic agent, if administered prior to events that might result in acute renal injury, such as surgery. Clinical trials are clearly indicated.

One rationale for the use of growth factors in end-stage chronic renal failure is to reverse the catabolic state that accompanies this condition. Growth hormone (GH) has been administered to adults with chronic renal failure on hemodialysis and was shown to reduce urea generation and improve the efficiency of dietary protein utilization in these individuals. GH administration resulted in increased circulating IGF-I, and the actions of GH in this setting are throught to be mediated via IGF-I [5].

The potential for the use of IGF-I as a therapeutic agent to enhance kidney function in the setting of chronic renal failure is based upon clinical and experimental observations relating to actions of GH on the kidney [6]. In short, conditions of GH deficiency in man and in experimental animals are associated with a reduction of kidney size, glomerular filtration rate and renal plasma flow, and states of GH excess are associated with an increase in kidney size and enhancement of glomerular filtration rate and renal plasma flow. However, GH does not affect kidney function in the setting of renal insufficiency [7].

The actions of GH on the kidney are mediated through IGF-I. To determine whether humans with reduced kidney function are responsive to the renal effects of IGF-I, we administered IGF-I to patients with chronic renal failure and evaluated its effects on inulin and *p*-aminohippurate clearances. We showed that IGF-I increases glomerular filtration rate and renal plasma flow in these patients [4, 8]. Although much work remains to be done, and clearly caution is advised, our observations establish the potential for the use of IGF-I as a therapeutic agent in this setting.

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* The editors invite questions for this section