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The clinical spectrum of human hantavirus infection in Somerset, UK

J. V. S. PETHER[1] AND G. LLOYD[2]

[1] *Public Health Laboratory, Musgrove Park Hospital, Taunton, Somerset TA1 5DB, UK*

[2] *Viral Diagnosis Group, PHLS Centre for Applied Microbiology and Research, Porton Down SP4 0JG, UK*

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SUMMARY

The signs and symptoms exhibited by 29 patients with an acute illness in whom antibodies to hantavirus were detected are described. In the severe cases the most striking signs and symptoms were the persistence for 2 or 3 weeks of a severe sore throat with pyrexia that developed early in the illness, followed by swelling of the face, neck and extremities, with arthropathy and prolonged malaise that lasted for months. A macular erythematous rash, hepatomegaly with abnormal liver function tests, and a tendency to haemorrhage was a later feature of the severe cases. Mild cases presented with a variety of signs and symptoms that were very difficult to link together as a syndrome.

INTRODUCTION

Hantaan virus, the agent of Korean haemorrhagic fever (KHF), was isolated in 1976 from the lungs of *Apodemus agrarius*, the striped field mouse [1]. Haemorrhagic fevers with renal syndrome (HFRS) which resemble KHF have been described from China, Japan and the USSR with a mortality ranging from 5 to 20% [2]. A milder syndrome, nephropathia epidemica, with a mortality of less than 1% is caused by a related virus called Puumala virus and is endemic in Scandinavia [3–5]. The main rodent host for this virus is usually the bank vole, *Clethrionomys glareolus*. There are other serologically related viruses such as the Seoul virus [6], the rodent host of which is the rat, *Rattus rattus* or *Rattus norvegicus* and Prospect Hill virus [7], whose host is the American meadow vole, *Microtus pennsylvanicus*. Illness in humans, often called urban HFRS, associated with Seoul virus infection tends to be associated with a significant degree of liver damage and has a mortality around 5%. To date, no human disease has been associated with infection with Prospect Hill virus which is endemic in the United States.

Hantaan infections are world-wide zoonoses and human cases of varying severity have now been identified throughout most of mainland Europe [8–10]. Two acute cases were identified in Scotland in the 1980s [11, 12] and three reported patients have been diagnosed recently as suffering from acute hantavirus

infection in the county of Somerset, UK [13–15]. This paper describes the clinical features of illness in residents of Somerset that were associated either with the presence of IgM antibody to hantavirus in the early acute serum sample, or with the presence of IgG antibody that subsequently fell to $< 1:8$ over the following months.

MATERIALS AND METHODS

Survey

Fifty-seven general practitioners from 13 practices were visited to acquaint them with the signs and symptoms of the first three hospitalized cases of hantavirus infection and also to give them an overview of the literature on HFRS. From January to November 1992, patients who presented with fever and one or more signs and symptoms of the those first three cases were investigated for the presence of antibody to hantavirus. Additional clinical and personal information was collected, in particular the occupation and hobby of the patient. Clinical details from 80 request forms which accompanied blood samples submitted to the laboratory in the 6 months prior to the first case (August 1991) were examined for possible links with hantavirus infection. Similarly, during the 9 months (January–June 1992) 400 sera were tested for antibody to hantavirus when the clinical details raised a suspicion of hantavirus infection.

Serological methods

IgG and IgM antibody specific for hantavirus were detected by indirect immunofluorescence [16, 17] using viral antigens from virus serotypes 76–118 (the prototype Korean strain), Puumala (a Scandinavian strain), Cg 13891 (a Belgian strain) and Seoul (a Korean strain).

RESULTS AND DISCUSSION

The three hospitalized cases have been reported previously [13–15]. Examination of stored sera chosen on clinical grounds or the stated occupation of the patient revealed 7 out of a total of 80 sera with an antibody titre $\geqslant 16$, acquisition of which could be related to an acute illness and was followed by a fall to a titre of < 16. One hundred and thirty serum samples submitted by the 57 general practitioners in the 9 months detailed above produced 5 acute cases, and examination of the 400 sera tested prospectively because the clinical information indicated possible hantavirus infection identified a further 14 probable cases. One case diagnosed retrospectively had been admitted to hospital. Another retrospective case had been mildly 'off-colour' for one day and had gone to his general practitioner because he was a sewage works designer and therefore carried a leptospirosis hazard card. These cards are routinely issued to all workers who come into contact with sewage. The advice given is that at the first sign of illness to report to the general practitioner. His stored serum had an IgG titre of 64 to hantavirus when tested by immunofluorescence which fell to 32 after 3 months and was undetectable after a further 9 months.

Table 1 details the signs and symptoms of illness presumed to be associated with

Table 1. *Signs and symptoms of 29 cases of hantavirus infection*

Sign or symptom	IgG+ & IgM+*	IgG+ only†	All cases (%)†
Pyrexia	3/4	17/19	20/23 (87)
Prolonged malaise	2/4	22/24	24/28 (86)
Headache/stiff neck	1/4	15/17	16/21 (76)
Influenza-like illness	1/4	13/17	14/21 (67)
Abnormal liver function tests	2/4	6/9	8/13 (62)
Bleeding, rectal or haematuria	3/4	3/6	6/10 (60)
Persistent sore throat	1/4	6/9	7/13 (54)
Arthralgia: prolonged	2/4	7/13	9/17 (53)
Swollen face, neck or extremities	3/4	9/22	12/26 (46)
Anorexia	2/4	4/9	6/13 (46)
Myalgia	1/4	9/18	10/22 (45)
Proteinuria	3/4	0/3	3/7 (43)
Lymphadenopathy	2/4	7/18	9/22 (41)
Nausea, diarrhoea, vomiting	2/4	3/11	5/15 (33)
Rash	3/4	5/12	8/26 (31)
Abdominal/loin pain	2/4	4/16	6/20 (30)
Chest pain, breathlessness	3/4	2/13	5/17 (29)
Itching, sweating	2/4	2/12	4/16 (25)
Hepatomegaly	2/4	2/13	4/17 (24)
Dizziness	0/4	4/14	4/18 (22)
Conjunctivitis	1/4	3/16	4/20 (20)
Frequency	0/4	1/4	1/8 (13)
Jaundice	1/4	1/18	2/22 (9)

* One person, the father-in-law of the first reported case, had IgG and IgM antibody but had had no illness in the past year.

† In some cases it was not possible to obtain full clinical details, and some patients were lost to follow-up.

acquisition of antibody to hantavirus. Three of the four cases with IgG and IgM antibody have already been reported. The fourth case was the father-in-law of the first case (August 1991) and did not admit to any obvious illness in 1991. In the third column are details of the clinical spectrum of the further 25 cases, one of whom needed hospital admission with a swollen neck, hands and feet and extensive lymphadenopathy and abdominal pain. Two cases still had antibody at a titre of $\geqslant 16$ to hantavirus 9 and 12 months after the initial illness; the significance of this is uncertain [18]. No case had any serological evidence of antibody to influenza A or B, respiratory syncytial virus, *Mycoplasma pneumoniae*, *Coxiella burnetii*, chlamydial antigen, adenovirus or *Leptospira* sp. nor did they have agglutinins to brucella. However, while none of the patients with hantavirus antibody described here had a positive Paul–Bunnell, a subsequent case who came to the UK from the Middle East with active hantavirus infection had a false positive Paul–Bunnell that was identified by Epstein–Barr serology as past infection.

The emerging picture seems to be that hantavirus initially produces in some individuals an influenzal illness (67%) often with a prolonged pyrexia (87%) and headache (76%), infrequently requiring admission to hospital. Severe cases may develop a sore throat (54%) that persists for 2 or more weeks followed by swelling of the face, neck, hands and lower limbs often extending in a centripetal fashion and associated with a macular erythematous rash. There may also be enlargement

of the cervical and inguinal lymph glands. In one case [14] a biopsied cervical lymph gland was histologically indistinguishable from a T-cell lymphoma of angioimmunoblastic type; a diagnosis confirmed at the time by the histopathology panel of the Royal College of Surgeons. The case has recovered with no evidence of tumour. Hepatomegaly (24%) with abnormal liver function tests (62%) may occur and microscopic haematuria or detectable blood in the stools was observed in some cases. Mild cases may present with any of a variety of signs and symptoms that would be very difficult to recognize as an acute virus infection. As exemplified in the third reported case [15], the diagnosis could be confused with connective tissue diseases characterized by a presumed hypersensitivity vasculitis. This raises the question of the cause of this group of diseases; so far unidentified.

The lack of detectable IgM to hantavirus may be explained in two ways. Firstly, samples of blood from patients who did not need hospital admission are usually obtained late in the illness. Secondly, we do not know the relation of the indigenous virus to the available viral antigens and were therefore possibly not testing for homologous antibody. In none of our cases was any other diagnosis finally made, and the time relationship, together with the subsequent fall in antibody, substantiated our diagnoses. In one report specific IgM levels were significantly higher in patients with severe disease than in patients with mild disease [19]. Residual antibody many years after the presumed primary infection may reflect the intensity of the original exposure [18] or chronic infection by the virus. In the past, workers identifying hantavirus infection for the first time in a country found only low levels of antibody [18, 20–24]. However, when sera were tested against the indigenous virus isolate, the levels were markedly higher [25].

The source of this aerosol-borne virus was apparent in most cases. Nine patients worked on farms, 4 worked with sewage or were designers of sewage works, 8 lived or worked in areas where rats had been observed or had hobbies that brought them into close proximity with rat-infested areas, and 3 lived or worked near to a particular sewage works that was greatly overloaded and rat-infested. Attempts are being made to isolate hantavirus from rodents in Somerset. Currently, hantavirus antibody has been identified in 4 of 100 rats, 1 of 102 mice but in none of 76 bank voles. Lungs and kidneys from all these rodents are to be cultured for hantavirus.

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