CASE REPORT

Hantavirus: an infectious cause of acute kidney injury in the UK

Kate Adams,¹ Lisa Jameson,² Rolf Meigh,¹ Tim Brooks²

¹Department of Infection, Castle Hill Hospital, Cottingham, East Yorkshire, UK
²Rare and Imported Pathogens Laboratory, Salisbury, Wiltshire, UK

Correspondence to
 Dr Kate Adams,
 kate.adams@hey.nhs.uk

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SUMMARY

We present a case of an undifferentiated febrile illness in a 59-year-old man from East Yorkshire. He was initially treated for leptospirosis due to the fact that he had farm exposure and the findings of acute kidney injury (AKI), thrombocytopenia and a raised alanine transferase (ALT) on his initial blood results. Serology tests later proved him to have had another rodent-borne illness: hantavirus. An investigation by Public Health England (formerly known as Health Protection Agency) (PHE) went on to prove the presence of the same serotype of hantavirus in rats caught on the patient's property. After an initial deterioration, the patient made a relatively uneventful recovery and all his blood tests returned to normal levels.

BACKGROUND

Hantavirus is a recognised cause of acute kidney injury (AKI) and has been listed as 1 of the 15 major factors leading to a rise in absolute incidence of AKI throughout the Western world.¹ Although common in Europe, there have been relatively a few recent case reports of hantavirus in the UK other than those associated with exposure abroad.² In the absence of a travel history the diagnosis is rarely if ever thought of or tested for by general practitioners (GPs) or hospital physicians. It is our opinion that hantavirus is underdiagnosed in the UK and should be considered in the differential diagnosis whenever leptospirosis is considered. Our case report in conjunction with the isolation of the virus from rats caught on the patient's property strongly supports the presence of a pathogenic UK hantavirus. It is our hope that this case report will increase awareness of hantavirus as a potential diagnosis in the UK. Experience from other endemic countries shows that early diagnosis of hantavirus provides a twofold benefit: (1) reducing the cost of unnecessary treatment and (2) improving the clinical outcome for the patient. Where clinical awareness is high the need for dialysis as a treatment for hantavirus-induced AKI has fallen to less than 5%. Complications such as hyperkalaemia and severe uraemia can often be avoided with careful fluid balance.³ In Europe, patients with early and correct diagnosis were significantly less likely to be hospitalised and given inappropriate antibiotic treatment compared with those with a delayed diagnosis.⁴

CASE PRESENTATION

In December 2011, a 59-year-old man presented to Hull Royal Infirmary with a 2-day history of fever, rigours, anorexia and a dry cough. He lived

on a small hold farm in East Yorkshire. Approximately 2 weeks prior to admission, he had been treated with oral flucloxacillin by his GP for mild cellulitis following a cut to his wrist on some metal in a pig field. The wound had initially gone unnoticed by the patient and therefore there was some exposure of the wound to the dirt and untreated water in the pig field. Along with pigs, there were horses and cows on the farm and with hindsight the patient and his wife noted that there had been an increase in the numbers of rats seen around the farm in the weeks prior to his illness. He had a medical history of psoriasis and pulmonary sarcoidosis, which was quiescent and he was on no regular medication. He had no travel outside the UK for at least 3 years. Apart from a temperature of 38.1°C, examination on admission was normal. The wound on his wrist had completely healed with no residual signs of any cellulitis. The patient was transferred to the infectious diseases ward in Castle Hill hospital where further tests were performed.

INVESTIGATIONS

Initial blood results demonstrated AKI, deranged liver enzymes, lymphopenia and thrombocytopenia (table 1). His chest X-ray (CXR) was clear. Three sets of blood cultures were negative, as was a throat swab for respiratory viruses and urinary *Legionella* antigen.

During his admission hepatitis A, B, C and E and *Leptospira* serology were checked and were all negative. Owing to the clinical picture and the farming history, blood was sent to Rare and Imported Pathogens, Public Health England (PHE), Porton Down for hantavirus serology. Serum was confirmed strongly positive particularly to Seoul and Hantaan IgM (strip-immunoassay) and IgG (immunofluorescence assay, IFA) as detailed in table 2. Serology was repeated 12 days later and pointed towards this being a Seoul serotype (1:40 000) by IFA. No detectable hantavirus RNA was found in either blood or urine samples. However, further circumstantial evidence that this patient's infection was caused by a Seoul hantavirus was provided when a subsequent PHE investigation isolated a new UK strain of Seoul hantavirus from rats on the patient's property.⁵

DIFFERENTIAL DIAGNOSIS

In cases of undifferentiated fever such as this there is generally a wide differential diagnosis including bacterial and viral infections, autoimmune processes and malignancy. Given this patient's previous

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Table 1 Selected blood results

	25/12/11	26/12/11	28/12/11	29/12/11	31/12/11	01/01/12	04/01/12	06/01/12	13/01/12	27/02/12
Haemoglobin, g/dL	16.1	15.4	15.5	14.6	14.9	14.2	13.1	12.5		14.0
White cell count $\times 10^9$ /L	2.6	4.5	7.1	5.5	5.8	6.6	9.4	5.7		6.0
Lymphocytes $\times 10^9$ /L	0.52	0.79	1.98							
Platelets $\times 10^9$	49	58	70	179	210	262	271	256		225
Prothrombin time, s		11.2			10.4	10.9	12.7	11.6		
APTT, s	32.2	30.2			22.4	23.8	26.9	26.4		
Sodium, mmol/L	131	131	129	129	136	139	136	141	142	140
Potassium, mmol/L	4.0	3.8	3.9	3.5	3.9	4.0	3.5	4.0	5.0	4.5
Bicarbonate, mmol/L	24	26	20	20	22	23	23	27	25	23
Urea, mmol/L	8.3	8.1	15.0	20.1	19.2	15.5	6.5	5.5	5.2	7.3
Creatinine, μ mol/L	132	144	299	378	333	277	148	134	131	96
Bilirubin, μ mol/L	20	20	41	57	38	26	22	19	13	13
Alkaline phosphatase, iu/L	81	76	106	163	323	385	263	229	189	58
Alanine aminotransferase, iu/L	305	221	245	248	143	120	64	57	47	18
Albumin, g/L	32	30	26	26	22	21	22	23	29	39
CRP, mg/L	135	97	113	94	27	22	189	71	8.4	1.2

APTT, activated partial thromboplastin time; CRP, C reactive protein.

history of sarcoidosis a flare-up of this also needs to be considered. However, his farm exposure and in particular the history of his wrist injury in conjunction with the AKI, thrombocytopenia and deranged liver enzymes meant that the main differential diagnosis was leptospirosis.

TREATMENT

As leptospirosis was the working diagnosis he was given intravenous benzyl penicillin and oral ciprofloxacin. Initially, he remained unwell with a spiking temperature and his renal function deteriorated (see table 1). On day 4 his temperature settled and shortly afterwards his blood tests started to improve. The antibiotics were stopped and at his request he was discharged home for close outpatient follow-up. Shortly after discharge, he complained of increasing lower abdominal pain and his C reactive protein (CRP) rose sharply. A repeat CXR remained clear, urine culture was negative and a CT scan of his abdomen and pelvis was reported as being normal. His abdominal pain and CRP settled over the next few days without further intervention.

OUTCOME AND FOLLOW-UP

Over the next few weeks, he continued to make an uneventful recovery. By the end of February 2012, 2 months after the initial illness, all his blood tests had normalised. Interestingly as part of the PHE investigation following this case, all family members and farm workers had serology tests performed for hantavirus and all these subsequently came back negative.

Table 2 Results of patient's hantavirus serology

Serotype	06/01/12	18/01/12
Puumala virus	Positive 1:1000	1:1000
Dobrava virus	Positive 1:1000	1:3200
Sin Nombre virus	Positive 1:100	1:1000
Saaremaa virus		
Seoul virus	Positive 1:10 000	1:40 000
Hantaan virus	Positive 1:10 000	1:20 000

DISCUSSION

Hantaviruses are a group of over 40 rodent-borne viruses, which are globally widespread. Most hantaviruses can only be passed to humans through direct contact with rodents or material contaminated with rodent waste (urine and faeces).⁶ The disease presents in different forms with the severity and target organs largely dependent on the causative serotype: hantavirus cardiopulmonary syndrome (HCPS) in the Americas caused predominantly by infection with serotypes Sin Nombre (SINV) and Andes (ANDV) and haemorrhagic fever with renal syndrome (HFRS) caused predominantly by infection with Hantaan (HTNV) and Seoul (SEOV) in Asia and Dobrava (DOBV) and Puumala (PUUV) in Europe. The different serotypes are carried by different rodents. Most of the serotypes are carried by various species of mice or voles. In contrast, SEOV is carried by the brown rat *Rattus norvegicus*, which is widespread throughout Europe including the UK. Although there is some serological evidence of SEOV infection in Europe there have been very few proven human cases outside of Asia. To the best of our knowledge, our case is the first reported case of SEOV infection from a wild rat population in the UK.

The clinical course of HFRS is classically divided into five phases: febrile, hypotensive, oliguric, diuretic and convalescent.⁶ However, some or all of these phases may not be evident as HFRS can present as a spectrum from subclinical to fatal. Generally infections caused by HTNV and DOBV are clinically more severe than those caused by SEOV. PUUV is considered to cause only mild or subclinical illness. A large Chinese study of the different clinical characteristics of HTNV and SEOV infections found a significantly higher mortality rate and a higher requirement for dialysis in the HTNV group.⁷ Interestingly however, they found that patients with SEOV infection had a longer duration of fever and were more likely to have liver enzyme derangement, sometimes even in the absence of AKI. The lack of typical HFRS features in patients infected with SEOV also meant that they were more likely to be initially misdiagnosed. Other than in south-east Asia, where intravenous ribavirin has been demonstrated to be efficacious when given early, there is no specific treatment for HFRS.^{8 9} Management is supportive and careful fluid management is crucial. Severe cases may require renal replacement therapy.

Although widespread in Europe, there have been only sporadic reports of indigenous hantavirus cases in Scotland and England.^{10–17} Since 1980s there has been growing evidence for endemic hantavirus infection in the UK. Most recently there has been a case report of hantavirus infection in a patient in Wales.¹⁸ Interestingly serology from this case also pointed towards it being SEOV. Subsequently, SEOV RNA was detected from the patients two pet rats and from several others from a larger breeding pack in England that the pet rats had been sourced from.¹⁹ The evidence from our case and the Welsh case would seem to show that SEOV is present in both the wild and the pet rat populations in the UK and therefore there can be little doubt that it is also causing human infections. With recent reports of SEOV being detected in France²⁰ and pet rats in Sweden²¹ our findings are of interest beyond the UK.

Despite this hantavirus is rare if ever thought of as a diagnosis or tested for by GPs or hospital physicians in the UK. This case demonstrates the need for all frontline physicians to be aware of hantavirus as a potential diagnosis in patients presenting with fever, AKI and thrombocytopenia, particularly if there is a history of potential rodent contact. It should also be considered in cases of febrile illness with liver enzyme derangement with or without AKI. Indeed, it should be thought of and tested for whenever leptospirosis is a differential diagnosis.

Learning points

- ▶ Hantaviruses are a group of over 40 rodent-borne viruses, which can be spread to humans by close contact with rodents or material contaminated with rodent waste.
- ▶ There appears to be a new Seoul serotype hantavirus, which is present in the UK wild rat population and has the potential to cause human infections.
- ▶ Seoul serotype hantavirus cause a clinical picture of haemorrhagic fever with renal syndrome.
- ▶ Hantavirus should be considered as part of the differential diagnosis in patients presenting with fever, acute kidney injury and thrombocytopenia, especially if there is a history of possible rodent contact.
- ▶ Management of hantavirus is supportive and careful fluid balance is crucial.

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Competing interests None.

Patient consent Obtained.

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