International Journal of Infectious Diseases 79 (2019) 75–76

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Case Report

# Severe Sinus Bradycardia in Puumala virus infection

Andréa Pastissier[a], Sébastien Humbert[a,*], Pauline Naudion[a], Nadine Meaux-Ruault[a], Marc Badoz[b], Nadine Magy-Bertrand[a]

[a] Service de Médecine Interne, CHRU de Besançon, Besançon, France
[b] Service de Cardiologie, CHRU de Besançon, Besançon, France

ARTICLE INFO

*Article history:*
Received 17 September 2018
Received in revised form 25 November 2018
Accepted 26 November 2018
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

*Keywords:*
Hantaviruses
Bradycardia
Hemorrhagic fever with renal syndrome
Puumala virus
France

ABSTRACT

*Puumala orthohantavirus* (PUUV) is the most prevalent of the four species of zoonotic hantaviruses found in Europe, causing nephropathia epidemica, a mild form of hemorrhagic fever with acute kidney injury that presents with elevated serum creatinine level, proteinuria and hematuria. The febrile phase of the infection begins with flu-like syndrome and visual disturbance. Laboratory results can show thrombocytopenia. The oliguric phase with elevated serum creatinine level then occurs. Cardiac involvement is sometimes observed, especially ECG abnormality: transient T-waves inversion, generally in the lateral or inferior leads. Marked bradycardia has been exceptionally described. We report the case of a 36-year-old woman with acute PUUV infection. Two days after admission, the patient presented a sinus bradycardia at 25/min. The bradycardia was asymptomatic, persisted one week and resolved spontaneously. Cardiac involvement in Puumala virus infection seems not to be associated with a bad prognosis. Bradycardia in the course of an influenza-like illness in endemic areas should suggest several pathogens such as legionella, Q fever or PUUV virus infection.


## Introduction

Old world hantaviruses are mostly responsible for hemorrhagic fever with renal syndrome (HFRS). Among them, Puumala virus (PUUV) is involved in nephropathia epidemica (NE), a mild form of HFRS characterized by high fever, headache, backache, abdominal pain, transient blurred vision. The laboratory results can show thrombocytopenia and acute kidney injury with elevated serum creatinine level, proteinuria and hematuria (Vapalahti et al., 2003). Bradycardia has been reported in 36% of cases during NE, but severe bradycardia appears to be very rare (Pal et al., 2018). We report the case of a 36-year-old female who presented severe bradycardia during PUUV infection.

## Case report

In June 2017, a 36-year-old female patient without any past history saw a doctor for a five-day fever, muscle pain, and joint pain. Biological findings showed an increased C-reactive protein (CRP) level (230 mg/L), hemoglobin level was 10.4 g/dL, platelet count 70 10^9/L, and creatinine level 0.8 mg/dL. Bone marrow aspiration ruled out the hypothesis of malignant hemopathy.

The patient was admitted 48 h later for aphagia, persistant myalgia, and acute renal failure with a creatinine level of 4.5 mg/dL and a platelet count of 115 × 10^9/L. Heart rate was 45/min. Antinuclear antibodies were negative, blood cultures were sterile, proteinuria was 1.06 g/day. IgM against PUUV were detected using the Reagena POC® Puumala IgM test and PUUV infection was confirmed by real time RT-PCR by the French National Reference Center for Hantavirus (Kramski et al., 2007). Two days after admission, the patient presented an asymptomatic sinus bradycardia at 25/min with incomplete right bundle branch block, and normal corrected QT on the electrocardiogram (Figure 1). Rest and symptomatic treatment were provided. After five days, fever disappeared, creatinine level decreased 1.7 mg/dL, CRP was 8 mg/L and platelet count was 280 × 10^9/L. The patient, always asymptomatic, was discharged with a heart rate of 33/min, without any other modification on the electrocardiogram. Echocardiogram and electrocardiograph (ECG) performed two months later were normal with a heart rate of 60/min.

## Discussion

Hantaviruses are enveloped RNA viruses belonging to the family *Hantaviridae* (Order *Bunyavirales*), transmitted to humans by

* Corresponding author.
*E-mail addresses:* andrea.pastissier@gmail.com (A. Pastissier), shumbert@chu-besancon.fr (S. Humbert), pauline.naudion@gmail.com (P. Naudion), nmeauxruault@chu-besancon.fr (N. Meaux-Ruault), mbadoz@chu-besancon.fr (M. Badoz), nmagy@univ-fcomte.fr (N. Magy-Bertrand).

https://doi.org/10.1016/j.ijid.2018.11.019

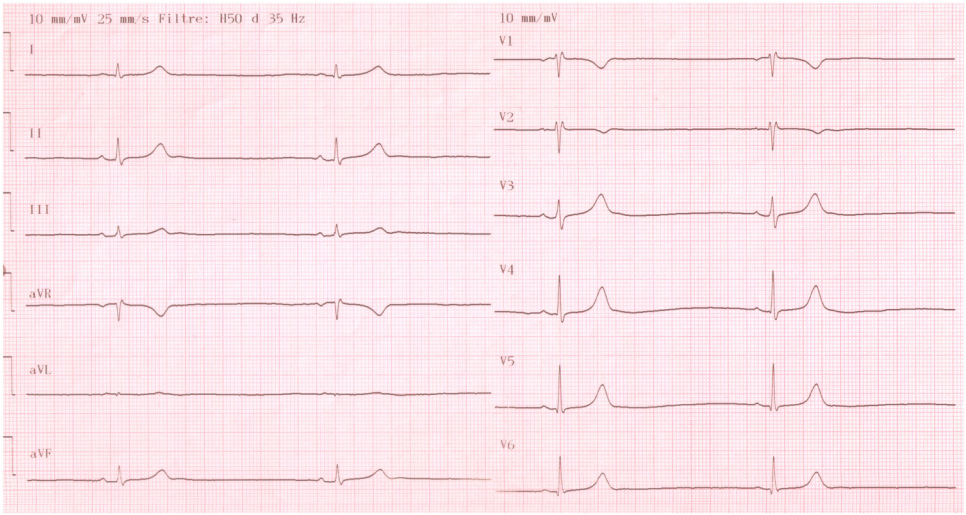


**Figure 1.** Sinus bradycardia occurred 9 days after first symptoms.

inhalation of rodent secretions. According to epidemiologic data, hantavirus infections are infrequent in France, with 14 to 253 cases detected per year between 2005 and 2016, following the three-year life cycle of those rodents (Heyman et al., 2011). During PUUV infection, the clinical course is characterized by several phases: febrile, hypotensive, oliguric, polyuric, and then convalescent. The febrile phase is marked by a flu-like syndrome and visual disturbance. In addition, thrombocytopenia is an important feature of HFRS (Jiang et al. 2016).

Cardiac involvement has been reported in one quarter to half of patients with PUUV infection (Mäkelä et al., 2009; Rasmuson et al., 2013). In a study of 70 patients with proved PUUV infection, Mäkelä and al. found 57% of ECG abnormalities (Mäkelä et al., 2009). The most frequent ECG abnormality was transient T-waves inversion, generally in the lateral or inferior leads. Furthermore, Kitterer and al. found that relative bradycardia (heart rate <90 bpm and fever) was present in four-fifths of patients in acute phase of PUUV infection, but no severe bradycardia was described (Kitterer et al., 2016). During an infection caused by the Seoul othohantavirus species, a marked sinus bradycardia (33 bpm) was described by Liu et al. in 2002, also with a good recovery (Liu et al., 2002). Severity of hantavirus infection is positively correlated to the age of the patients (Du et al., 2014). Furthermore, cardiac involvement in PUUV infection does not seem to be associated with a poor outcome. There is no specific antiviral treatment of PUUV infection. Even if early treatment with ribavirin reduces mortality and severity of symptoms for certain species of hantavirus, no previous study has proven sufficient efficacy and safety of ribavirin in PUUV infection (Malinin and Platonov, 2017). According to Cunha, relative bradycardia in infectious diseases is a feature of several pathogens, notably legionella, Q fever or viral hemorrhagic fevers, after exclusion of drug-induced bradycardia (Cunha, 2000). To our knowledge, it is the first case of such a severe bradycardia during Puumala virus infection; bradycardia in the course of an influenza-like illness in endemic areas should suggest Puumala virus infection.

## Acknowledgment

We thank Jean-Marc Reynes, head of the National Reference Center for Hantavirus for providing the hantavirus species identification.

## Conflict of interest statement

All authors have fully disclosed any financial and personal relationships with other people or organizations that could inappropriately influence their work.

## Funding source

All authors declare no funding for this work.

## Ethical approval

Ethical approval was not necessary for this work. The patient was informed that her case would be published and agreed.

## References

Cunha BA. The diagnostic significance of relative bradycardia in infectious disease. Clin Microbiol Infect 2000;6(12):633–4.
Du H, Li J, Yu H-T, Jiang W, Zhang Y, Wang J-N, et al. Early indicators of severity and construction of a risk model for prognosis based upon laboratory parameters in patients with hemorrhagic fever with renal syndrome. Clin Chem Lab Med 2014;52(November (11)):1667–75.
Heyman P, Ceianu C, Christova I, Tordo N, Beersma M, Joao Alves M, et al. A five-year perspective on the situation of haemorrhagic fever with renal syndrome and status of the hantavirus reservoirs in Europe, 2005-2010. Euro Surveill 2011;16(36) pii: 19961.
Jiang H, Du H, Wang LM, Wang PZ, Bai XF. Hemorrhagic fever with renal syndrome: pathogenesis and clinical picture. Front Cell Infect Microbiol 2016;6(February) [Cited 19 October 2017]. Available from: http://journal.frontiersin.org/Article/10.3389/fcimb.2016.00001/abstract.
Kitterer D, Greulich S, Grün S, Segerer S, Mustonen J, Alscher MD, et al. Electrocardiographic abnormalities and relative bradycardia in patients with hantavirus-induced nephropathia epidemica. Eur J Intern Med 2016;33(September):67–73.
Kramski M, Meisel H, Klempa B, Krüger DH, Pauli G, Nitsche A. Detection and typing of human pathogenic hantaviruses by real-time reverse transcription-PCR and pyrosequencing. Clin Chem 2007;53(November (11)):1899–905.
Liu Y-H, Huang J-H, Hsueh P-R, Luh K-T. Hantavirus infection with marked sinus bradycardia, Taiwan. Emerg Infect Dis 2002;8(6):644.
Mäkelä S, Kokkonen L, Ala-Houhala I, Groundstroem K, Harmoinen A, Huhtala H, et al. More than half of the patients with acute Puumala hantavirus infection have abnormal cardiac findings. Scand J Infect Dis 2009;41(January (1)):57–62.
Malinin OV, Platonov AE. Insufficient efficacy and safety of intravenous ribavirin in treatment of haemorrhagic fever with renal syndrome caused by Puumala virus. Infect Dis (Lond) 2017;49(July (7)):514–20.
Pal E, Korva M, Resman Rus K, Kejžar N, Bogovič P, Kurent A, et al. Sequential assessment of clinical and laboratory parameters in patients with hemorrhagic fever with renal syndrome. PLoS One 2018;13(5)e0197661.
Rasmuson J, Lindqvist P, Sörensen K, Hedström M, Blomberg A, Ahlm C. Cardiopulmonary involvement in Puumala hantavirus infection. BMC Infect Dis 2013;13(1):501.
Vapalahti O, Mustonen J, Lundkvist A, Henttonen H, Plyusnin A, Vaheri A. Hantavirus infections in Europe. Lancet Infect Dis 2003;3(10):653–61.