

# Investigating the causes of kidney dysfunction in HFRS

August 26 2021

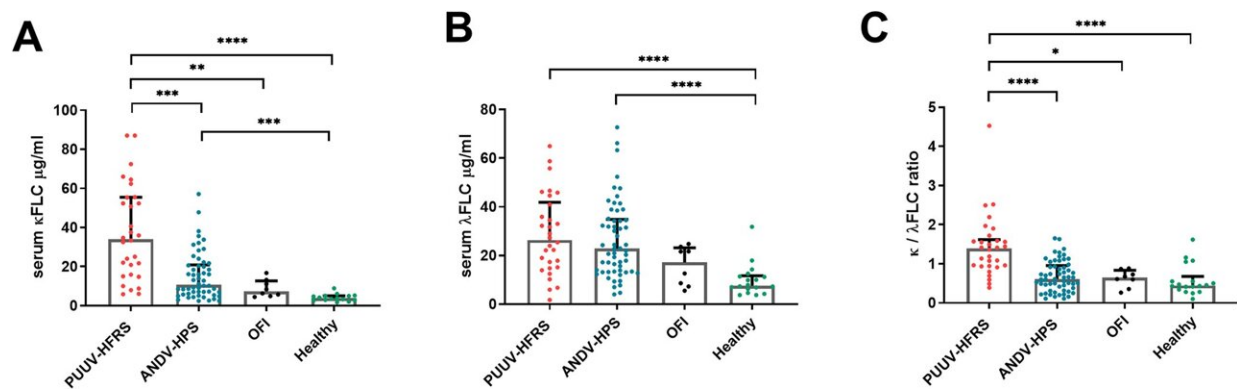


Fig 1. Soluble FLCs increase in hantavirus diseases. The concentrations of FLCs ( $\kappa$  in A and  $\lambda$  in B) as well as their ratio (in C) were measured by ELISA from serum samples of acute PUUV-caused HFRS ( $n = 30$ ), ANDV-caused HPS ( $n = 50$ ), other febrile illness (OFI;  $n = 8$ ) and healthy volunteers ( $n = 18$ ). The medians of patients with acute PUUV infection and OFI were compared to medians of healthy volunteers by Kruskal-Wallis + Dunn's multiple comparisons test and significant differences reported as \* =  $p$

In Finland, a disease known as nephropathia epidemica, a mild form of haemorrhagic fever with renal syndrome (HFRS) is caused by the Puumala virus (PUUV), which is a member of the family Hantaviridae. In addition to Finland, Puumala virus is endemic in northern Europe and Russia. Hantaviruses found elsewhere in the world if transmitted to humans can cause either a severe HFRS or the hantavirus cardiopulmonary syndrome (HCPS), both of which are more severe than the infection caused by PUUV.

In addition to influenza-like general symptoms, the clinical picture of HFRS includes [kidney](#) dysfunction, whose pathogenetic mechanisms are not known in detail. Antibodies are molecules called immunoglobulins, which are polypeptides/proteins composed of heavy chains which pair with [light](#) chains. Normally, human B [cells](#) responsible of immunoglobulin expression produce a slight excess of light chains that circulate free from the heavy chain in blood. The physiological role of free light chains is not well known, but in certain diseases, the accumulation of free light chains causes kidney dysfunction.

In a recently completed study, researchers at the University of Helsinki investigated whether patients suffering from mild HFRS have more free light chains in their circulation and whether their concentration was associated to kidney problems. The researchers also studied what, in the first instance, triggers the brief overproduction of free light chains in conjunction with hantavirus infection.

"The role of free light chains in [infectious diseases](#) has been not been studied much. In a prior study, we demonstrated that free light chains can be used to establish from urine that a patient with mild HFRS has antibodies against the virus. Now, we sought to investigate whether there is a general upregulation of free light chains in acute hantavirus infection," says Jussi Hepojoki, docent of virology and Academy of Finland research fellow at the University of Helsinki.

## **Puumala virus impairs antibody production**

The datasets that the researchers used consisted of serum and [urine samples](#) collected from hospitalized NE patients as well as kidney biopsies taken from similar patients in the 1970s and the 1980s provided by Tampere University Hospital. From Argentina, the researchers obtained results for clinical samples of patients who had suffered from a serious HCPS-causing Andes virus infection. In addition, the dataset included B cells from healthy donors.

By employing the clinical samples and cell culture experiments, the researchers demonstrated that the Puumala virus elevates the level of free light chains, which matches the severity of the disease and the related kidney dysfunction. In other words, the results indicated a link between elevated free light chain levels and

kidney dysfunction.

"We found B cells, which are a part of the immune system, in the patients' kidneys. In such situation, the B cells potentially produce extremely high levels of free light chains locally. The local overproduction of free light chains may be one of the mechanisms inducing kidney dysfunction," says Tomas Strandin, docent of virology and Academy of Finland research fellow at the University of Helsinki.

The study further shows that the Puumala virus is capable of directly infecting B cells, which is a new observation. B cells infected with or exposed to the virus commence the production of antibodies, simultaneously increasing the production of free light chains.

Previously, Swedish researchers demonstrated a connection between the disease and certain B cell lymphomas in another NE dataset. The activation of B cells caused by the virus can also shed light on the mechanisms associated with the link to lymphoma.

"It appears that the virus can also directly impair the assembly of antibodies/immunoglobulins on the cellular level, consequently impairing the efficiency of antibody production. Puumala virus, much like other hantaviruses, causes a persistent life-long infection in the bank vole, the natural host. This means that the [virus](#) must have mechanisms with which to overcome the body's immune response," Hepojoki says.

The researchers believe the elevated free light chain levels can play a role also in other infectious diseases, particularly zoonotic infections whose pathogens are capable of causing a persistent infection in their host.

**More information:** Jussi Hepojoki et al, Hantavirus infection-induced B cell activation elevates free light chains levels in circulation, *PLOS Pathogens* (2021). [DOI: 10.1371/journal.ppat.1009843](https://doi.org/10.1371/journal.ppat.1009843)

Provided by University of Helsinki

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