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Lack of evidence for an association between hantavirus
infections and Wegener’s granulomatosis, microscopic
polyangiitis, Churg–Strauss syndrome and giant cell arteritis

Sir. Systemic vasculitides are a heterogeneous group of
disorders characterized by inflammation of vessel walls.
Much progress has been made in understanding their
pathophysiology and pathogenesis, but the cause
remains unclear in the majority of the cases. Associations
with distinct viral infections have been demonstrated [1]. Among agents that have been implicated are
hantaviruses, the infectious causes of haemorrhagic
fever with renal syndrome (HFRS) and hantavirus
pulmonary syndrome [2]. HFRS occurs worldwide and
may be clinically inapparent. Hantaviruses are known
to infect endothelial cells in vitro and in vivo, inducing
acute vascular inflammation [3]. Moreover, there is evidence
that they can generate the formation of immune
complexes [4]. However, it remains obscure whether
hantavirus infections are involved in the development of
chronic vascular inflammation. We therefore investi-
gated the prevalence of hantavirus-specific antibodies
in a large group of patients with well-defined forms of
systemic vasculitides.

The sera studied were collected from patients attend-
ing the Departments of Rheumatology in Bad Bramstedt (Rheumaklinik) and Lübeck (University of Lübeck), Germany, between 1994 and 1998. These were
101 patients with Wegener’s granulomatosis (WG) and
30 patients with microscopic polyangiitis (MPA),
Churg–Strauss syndrome (CSS) and giant cell arteritis
(GCA), classified according to the definitions of the
Chapel Hill Conference and the classification criteria
of the American College of Rheumatology [5, 6]. Control
sera were obtained from 69 patients with rheumatoid
arthritis (RA) who fulfilled the American College of
Rheumatology criteria [7], and from 238 healthy
blood donors (Table 1). Patients and controls were
resident in northern Germany. Antineutrophil cyto-
plasmic antibody titres >1:8 determined by indirect
immunofluorescence were regarded as positive.

The enzyme-linked immunosorbent assay (ELISA)
for the detection of hantavirus-specific IgG antibodies
was performed as described previously [8]. Briefly, micro-
titre plates (Nalge Nunc International, Alberslund,
Denmark) were coated overnight at 4°C with a basic
buffer detergent extract of Puumala or Hantaan-
infected Vero cells inactivated with 2 × 10⁶ rad from a
⁶⁰Co source. Standard methods were followed, and
uninfected antigen controls were run for each serum.
Subsequently, wells were incubated with human serum
followed by a polyclonal antibody against human IgG
conjugated to horseradish peroxidase (Dako, Hamburg,
Germany), each for 1 h at 37°C. Substrate solution
(Kirkegaard & Perry Laboratories, Gaithersburg, USA)
was added for 30 min at 37°C and signals were
measured by spectrophotometry [optical density at
410 nm (OD₄₁₀)]. To yield the adjusted OD (aOD)
value, the reading of the negative control antigen
was subtracted. The cut-off was defined as aOD
0.100. All sera reacting positively in a 1:100 dilution
were tested again in a twofold serial dilution. Serum
titres ≥ 1:400 were considered as seropositive if the
added aOD₄₁₀ values of positively reacting serum
dilutions exceeded 1.0.

A total of 191 sera obtained from patients with
different forms of systemic vasculitides were tested,

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<th>Table 1. Demographic data and hantavirus screening of patients and blood donors</th>
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<tr>
<td><strong>n</strong></td>
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<tr>
<td>Blood donors</td>
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<tr>
<td>Rheumatoid arthritis</td>
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<tr>
<td>Wegener’s granulomatosis</td>
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<td>Microscopic polyangiitis</td>
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<td>Churg–Strauss syndrome</td>
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<td>Giant cell arteritis</td>
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NT, not tested.
ANCA, antineutrophil cytoplasmic antibodies.
including 30 from patients with localized WG. None of them displayed IgG antibodies to Puumala or Hantaan viruses. This was also true for 69 sera from patients with RA and 238 sera from healthy blood donors (Table 1). Control measurements of sera from patients with clinically apparent Puumala or Hantaan infections confirmed the validity of the assay used.

To the best of our knowledge, this is the first comprehensive study investigating the prevalence of hantavirus-specific antibodies in patients with systemic vasculitides. In our well-defined population of 191 patients with WG, MPA, CSS and GCA, we found no serological evidence of an association between hantavirus infections and the development of systemic vasculitides. The lack of positive sera among patients and controls suggests a low prevalence of hantavirus infections in the northern German population in general. However, the specific rodent reservoirs (Clethrionomys glareolus, Apodemus agrarius) are present and clinical cases of acute hantavirus infections (Puumala and Dobrava) are seen at the Lübeck University Hospital.

Antibody titres may decrease after the infection has resolved. Thus, we might have missed previous hantavirus infections in some cases. To minimize this bias we investigated sera from patients with short-term as well as those with longstanding disease. The lack of positive cases in both groups suggests that a time-dependent decrease in antibody titres was not a major problem. Moreover, previous studies have shown that elevated antibodies to hantaviruses generally persist for many years [9].

Our findings contrast with the results of a recent small uncontrolled study conducted in Bavaria, Germany. Among 26 patients with WG or MPA, Hierl et al. [10] detected antibodies to hantavirus in 15%. This high prevalence may be explained by their use of an immunofluorescence assay (Progen, Heidelberg, Germany), while we performed an internationally recognized ELISA [8]. Moreover, Hierl et al. used a cut-off titre of 1:16, resulting in relatively low specificity. In fact, none of their patients had a hantavirus antibody titre above 1:32.

In summary, our data indicate that hantavirus infections are not associated with the development of WG, MPA, CCS or GCA. Serological or molecular approaches might identify other infective agents in rheumatological disorders in the future.

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