

Clinical Characteristics of Ratborne Seoul Hantavirus Disease

Appendix

Appendix Table. Clinical characteristics of ratborne Seoul hantavirus disease*

Clinical symptoms common for HFRS, but also for HCPS

Premonitory complaints (3–5 d): sudden high fever, malaise, vomiting and diarrhea, severe **gastrointestinal pains**, mimicking acute appendicitis (1–4)

Headache and **influenza-like myalgiae**, but no premonitory upper airways symptoms evoking influenza: no rhinorrhea or throat ache
Initial eye pain and periorbital edema

Facial flushing, pharyngeal congestion (5)

(Micro-)hemorrhages, sometimes limited to conjunctival suffusion or intraoral petechiae† (5–8)

Dry cough, followed by **dyspnea** (7–14), outspoken and rapidly worsening in HCPS

Short-lived pseudo nephrotic syndrome:† despite massive proteinuria and frank hypoalbuminemia, conspicuous absence of generalized pitting edema (4, 12), hyperlipidemia, and thrombotic tendency

Clinical symptoms reported for HFRS, not for HCPS

Acute myopia (2–3 d) as a virtually pathognomonic, but transient sign (6, 7, 14); rarely acute bilateral glaucoma or retinal hemorrhage (15)

Severe **flank pain** (lumbalgia), sometimes unilateral, mimicking a renal colic (16, 17)

Rarely acute bilateral glaucoma or retinal hemorrhage (15)

Transient acalculous acute cholecystitis provoking right upper quadrant pain and a positive Murphy sign (18–20); considered a general severity sign (21)

Paradoxical sinusual bradycardia (<90 bpm), despite fever >38°C (6, 7)

Laboratory anomalies mainly reported for HFRS

Initial **thrombocytopenia** is the earliest and most constant sign‡ (4–6)

Urine spot PCR§ >0.11 plus microhematuria; early (mostly before hospitalization) and **rapidly evolving**, but cardinal sign, easy, and cheap to assess day-by-day

Hyponatremia and hypoalbuminemia, predicting clinical severity‡ (5, 8, 12, 22)

Highly increased levels of LDH, and particularly of CRP and PCT, mimicking hemolysis (18, 22) or a bacteria, rather than a virus, infection‡ (6–8)

Lipid paradox: low acute cholesterolemia (particularly decreased high-density lipoprotein-cholesterol levels), contrasting with fasting hypertriglyceridemia, both transitory (7, 18, 23, 24)

Serum creatinine levels might remain initially (18, 20) or constantly (4, 7, 25–27) at **standard levels**, or barely and briefly increased (28)

Slight-to-frank hypokalemia, despite often clearly impeded renal function (8, 29)

Ultrasound anomalies, reported more for HFRS than for HCPS

Third-space, protein-rich fluid effusions‡ (pleuritis, pericarditis, ascites)

Longitudinal renal diameter >11 cm¶ (17, 18), swollen cortex with echodensity greater than or equal to that for liver. Rare but virtually present or or absent pathognomonic sign: perirenal fluid rim

Transient hepatomegaly and splenomegaly (4, 8, 17)

AAC with mostly distended large gallbladder, and thickened (>4.5 mm) edematous gallbladder wall (18–21)

Liver involvement suggesting Seoul virus (SEOV) involvement

Aminotransferase levels increased to 10–20 times (or more) above the standard level (4, 12, 26) versus mild or no transaminitis in other HFRS forms (6–8); concomitant renal function impediment might be conspicuously absent (4, 7)

Rarely: icterus; can be pronounced, but is rapidly self-remitting (7, 30)

*All signs or symptoms are in present or absent chronologic order of appearance. Bold indicates a high diagnostic value. A general common feature is rapid self-remittance within days or weeks without leaving any sequelae (6). Ultrasound-documented renal shrinking within days is highly suggestive for HFRS. AAC acute cholecystitis; bpm, beats per minute; CRP, C-reactive protein; HCPS, hantavirus cardiopulmonary syndrome; HFRS, hemorrhagic fever with renal syndrome; LDH, lactate dehydrogenase; PCR, protein-to-creatinine ratio; PCT, procalcitonin.

†Rare to absent in HCPS, except in Andes virus (ANDV)-induced forms (5).

‡Also present in HCPS.

§Urine spot PCR, or urinary protein-to-creatinine ratio, is calculated in milligrams per deciliter or grams per liter; standard value for adults is <0.11. Urine spot PCR is also a surrogate for 24-h protein excretion in g/day, indicating that a urinary protein-to-creatinine ratio >3.5 is nephrotic-range proteinuria or equivalent to a dipstick value of +++(+).

¶Standard range 11–12 cm depending on body size. Ultrasound-documented renal shrinking within days is highly suggestive for HFRS

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