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Review Article

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Hantavirus Infections with Renal Involvement do not Result in Chronic Renal Disease or End-stage Renal Failure

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Abstract

Rodent-borne hantavirus infections are one of the most important causes worldwide of acute kidney injury in previously healthy, mostly young adults, but remain still heavily underestimated as such by the global nephrological community. Despite of a sometimes severe impairment of renal function, often accompanied by massive proteinuria, this acute zoonotic affection has, after survival, an excellent renal and general prognosis on short and on long term. However, this fact remains contradicted by repeated and unproven statements of the opposite in literature. Indeed, with the advent of early hantavirus research in the '80's, speculations rose as to the potential of this novel agent to cause chronic renal disease, and even end-stage renal failure, since the bulk of pathogenic hantaviruses has the human kidney as main target organ.

In several sections of this review, the authors try to dismantle point by point these unjustified assumptions. Finally, they show that in two recent Finnish retrospective studies on a local form of hantaviral acute kidney injury, nor the degree of acute renal impairment, nor the degree of acute but transient proteinuria, had any negative impact on the good renal outcome. These two studies, including the most important cohort numbers so far for the two specific questions, confirm an increasing series of case-reports or clinical overviews of hantavirus infections, all showing a good renal prognosis.

The generally somber prognosis for acute kidney injury during hospitalization, as expressed in numerous publications based on Kidney Disease: Improving Global Outcomes (KDIGO), should be reviewed for the peculiar case of hantavirus infections.

Keywords

Hantavirus; Hemorrhagic fever with renal syndrome; Nephropathia epidemica; End-stage renal failure; Community-acquired acute kidney injury; Chronic kidney disease of unknown etiology

Introduction

Hantaviruses (HTV's) are emerging viruses, some of which elicit in humans sudden fever followed by multiple organ dysfunction syndrome (MODS), targeting mainly the kidney (acute kidney injury or AKI) and/or lung (acute lung injury or ALI). HTV pathophysiology is now generally accepted as being an over responsive immunoreaction, targeting the endothelium in the human host, triggered after a sometimes very brief period of viremia [1,2]. This micro vascular leakage, which can result is massive protein-rich fluid accumulation in third spaces (ascites, pleuritis, pericarditis and/or generalized interstitial edema) is extremely rapid, but also rapidly and spontaneously self-remitting within the course of 2-3 weeks. Pathologic HTV's are spread by rodents, excreting probably life-long infectious viral particles, which may be inhaled by humans, thus causing infections, showing the full spectrum of being severe, mild, or asymptomatic, isolated, in local outbreaks, or even in massive epidemics. Moreover, fatality rates in all these modalities range between 0, 5 up to 35 %, depending on the infecting HTV species and the human immune response [1,2].

From the pioneer times on of hantavirus discoveries, i.e. the early '80's, initial research was excited by the idea that this novel renotropic pathogen could perhaps explain then unclarified but chronic renal alterations, ending eventually even in end-stage renal failure (ESRF), requiring chronic haemodialysis therapy, or other forms of chronic renal replacement therapy (RRT). The purpose of this review is to put some question marks after this hypothesis, which was never convincingly proven so far, but is nevertheless still invoked in many hantavirus reviews or articles, even currently and in major nephrology journals.

Global epidemiology of hantavirus infections

HTV endimicity is closely linked worldwide to the presence (or not) of a specific biotope suitable for a specific rodent reservoir-carrier, explaining the sometimes outspoken geographic differences in incidence, and explaining also for instance the paucity or complete absence of HTV infections in South-Europe, with a noticeable exception for the Balkans [1,2]. Another consequence is that most hantavirus infections are a quintessential example of community-acquired AKI (CA-AKI), targeting mainly a predominantly male, young adult (mean age about 40 years) and previously healthy population, with a professional exposure to wild rodents, such as farmers, military, game keepers, etc. Inevitably, a first but important confounding factor for epidemiological studies, weighing the increasing importance of global AKI, is that the bulk of these cases are hospitalized for initially non-renal complaints (fever, abdominal pain, vomiting, etc.), and that underlying but rapidly progressive AKI is discovered only in the hospital, blurring the lines between CA-AKI and true hospital-acquired-AKI (HA-AKI) [2]. Nevertheless, hantavirus infections cannot longer be dismissed by the western nephrological community as an esoteric, or even exotic, problem, since it is the most important global zoonosis after its great imitator leptospirosis, with a currently estimated incidence of 150,000 up to 200,000 AKI cases per year, particularly in China [2]. Indeed, an under-evaluated but impressive data bank is the Chinese hantavirus registry (http://www.chinacdc.cn/en/), assessing yearly hantaviral AKI epidemics, notifiable remarkably enough already since 1950 [3]. Through 2014, this yielded an unsurpassed total of 1,625,002 cases, and 46,968 (2.89 %) fatalities. Peak year was 1986, with 115,804 cases [3]. Mostly milder forms are likewise well-established in Western Russia, totalling 245,093 cases (1978-2015), again a fact underestimated even

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in current hantavirus literature (http://rospotrebnadzor.ru/activities/statisticalmaterials/statictic_details.php?ELEMENT_ID=5525). Finland, with 40,839 cases (1979-2015), renders this European Union (EU) member as in fact the most endemic country in the world, with hantaviral AKI as the single most important current cause of AKI altogether (https://www.thl.fi/ttr/gen/rpt/tilastot.html). Other EU countries with rapidly growing incidences are Germany (total 2001-2016: 10,049 https://survstat.rki.de/Content/Query/Create.aspx) and Belgium (total 1983-2015: 3,313), (www.wiv-isp.be), perhaps as a result of global warming [2,4,5].

After the isolation by Lee et al. in 1976 [6] of the prototype hantavirus, the Korean Hantaan virus (HTNV), western medicine discovered in the early '80's that HTNV-like, but genetically different pathogenic agents were present in Fenno-Scandia [7-11], and in the Americas [12]. After a 1983 World Health Organization (WHO) meeting, the "novel" disease was coined as "hemorrhagic fever with renal syndrome" (HFRS), consisting of sudden fever, severe lumbalgia, AKI, (previously incorrectly denominated as acute renal failure or ARF), and thrombocytopenia [13]. Although never exactly defined as such, the "renal syndrome", constituting the salient clinical feature of HFRS, has been described to be accompanied by initial but transient acute proteinuria and microscopic haematuria, all items easy and quick to verify. Already in this historical 1983 WHO report, it was noted that "Survivors…. usually make a complete recovery. Long-term sequelae are rare". Moreover, it became quickly clear that epidemics of apparently the same disease had been described centuries before in China, and decades before in Fenno-Scandia [14].

The pioneer role of Fenno-Scandia and its hantaviral prototype Puumala virus

As early as in 1934, and in Sweden, recurrent outbreaks of a febrile kidney disease had been noted, later aptly nominated as "nephropathia epidemica" (NE) [15]. However, NE was subsequently disregarded by the nephrological community as a local Scandinavian curiosity, until Lähdevirta described, in the '70's and in Finland, this "novel" disease in virtually all its aspects, even before the etiological viral agent was actually known [16]. Of note, Lähdevirta found no substantial renal clinical sequelae of NE, not even in repeated renal biopsies in nine patients 4-5 years after the acute phase. To cite this founding father of clinical hantavirology: "The study shows that practically complete and lasting clinical recovery follows the acute phase of nephropathia epidemica, and that the disease does not leave diagnostic structural changes in the kidneys" [17]. Finally, the etiological agent was isolated in 1984 from a wild rodent, the bank vole (*Myodes glareolus*), very common in North–and West-Europe, and called Puumala virus (PUUV). Antigens from the Asian prototype HTNV, the European prototype PUUV, and the global rat-borne Seoul virus (SEOV) [10-12] allowed now worldwide serological confirmation of presumed acute AKI caused by hantaviruses through IgM demonstration, and previous HFRS (or NE) by IgG detection, since these neutralizing antibodies may remain detectable lifelong, following acute infection [18,19]. In all above named countries, important late-onset renal complications were to our knowledge never reported so far in case-controlled or epidemiological series. In the biggest European sero-epidemiological study to date, comprehending a total of 21,059 healthy Belgian civilian and military blood donors, immunofluorescent assay (IFA) screening with HTNV and/or with PUUV yielded 275 IgG positives, or a prevalence of 1.30 %. A complete renal staging, including blood and urine examination and renal echography, in 64 military PUUV-IgG positives revealed no abnormalities, and no elevated blood pressure (BP). Moreover, none of these study subjects recalled a prior hospital admission for AKI [2,20]. However, one recalled study subject, belonging to an elite para-commando unit, showed repeatedly pathologic proteinuria and microscopic hematuria, together with increasing arterial hypertension. Further follow-up confirmed declining renal function, prompting a renal biopsy demonstrating IgA nephropathy. This patient ended ultimately in chronic hemodialysis, and received a renal transplantation (Clement, unpublished observations).

In professional groups under close follow-up, such as the Army, it is improbable that long-term renal sequelae would go unnoticed for years, after an acute affection that is moreover typically induced by military activities on the field [21-23]. Of note, the 1990 AKI outbreak near Ulm in South-Germany was the first documented PUUV outbreak in that country, affecting moreover only PUUV-naïve US military [22]. The renal outcome in the 14 hospitalized soldiers was favorable and rapid, as usual (Clement, unpublished observations). As for the civilian sector, if such long-term renal sequelae would be present indeed, national health institutions would have detected in highly endemic countries such as Finland an unexplained surge of renal compromise with or without arterial hypertension in an age group normally not at risk, i.e. starting at 40 years, or even younger. No such observations are currently at hand.

Chronic hemodialysis patients and the case of North-Ireland and Africa

Another favorite of early HTV research was to seek in chronic hemodialysis patients a correlation of former HTV infection and the life-long need of RRT. However, all cited studies pertained solely to hantavirus IgG seropositivity, since study subjects were not questioned as to a prior AKI episode with hantaviral characteristics, nor to any prior nephrological follow-up, including or not a renal biopsy. This means that the first arm of such studies implied that even an asymptomatic HTV infection without noticeable AKI episode was putatively linked to ESRF, needing chronic RRT, thus presumably after a smouldering years-long subclinical evolution. From the start, this hypothesis was invalidated with a 1983 Belgian study, showing PUUV seropositivity in only 0.7 % of 596 screened patients in chronic hemodialysis, and contrasting with the much higher 1.3% seroprevalence in a substantial, asymptomatic, and healthy Belgian control group (see section 3) [24]. However implausible such a hypothesis remained from a purely nephrological point of view, it was verified all over the world, giving in all other countries less than convincing results. We cite in chronological order, with the obtained seroprevalence between brackets: 1985 United Kingdom (0.5%) [25], 1988 North-Ireland (9%) [26], 1993 USA (2.76%) [27], 2004 Egypt (1.4%) [28], 2007 Lithuania (7.4 %) [29], 2010 Czechia (1.7%) [30]. In all these studies, the HTV seropositivity rate in hemodialysis patients was not significantly higher than that in the general healthy population or not compared to such control group (USA). The North-Irish result of 9% is divergent, because pertaining only to 8/90 farmers, and screened not by PUUV, but by a SEOV strain (R22), obtained from a wild rat captured in the Henan province, China. Indeed, North-Ireland is the only region in Europe totally devoid of all rodent reservoirs of hitherto known pathogenic HTV's , except SEOV. Thus, a subsequent (1993) sero-epidemiological study with 9 different strains of live pathogenic HTV's, including 2 SEOV strains, (R22 and Tchoupitoulas or TCHV), 4 other murine hantaviruses, and 3 arvicoline hantaviruses (including PUUV), an almost exclusive reaction was found against the same IFA screening

antigen R22, yielding an overall SEOV seropositivity of 2.06 %, or 15/727 (627 clinical samples and 100 asymptomatic controls) [31]. Of note, all these 15 seropositives were again North-Irish farmers, living in County Down, but formerly hospitalized with a suspicion of leptospirosis, given the presenting symptoms of fever, AKI and thrombocytopenia. Since however serology for leptospirosis and the eight other pathogenic HTV's remained negative or atypical, these 15 patients should be considered as the first European clinical series of SEOV-nephropathy. Here again, the renal outcome was excellent, although SEOV is generally considered as causing more severe HFRS cases than PUUV [1,2] (Clement, unpublished observations).

The Egyptian 2004 study is noteworthy, because a "novel" agent was screened as putative origin of ESRF, needing chronic RRT, whereas to our knowledge, no fully documented autochthonous clinical case of hantaviral HFRS, confirmed with RT-PCR and/or neutralization tests, has been reported hitherto from the continent Africa. The Egyptian study enrolled 350 patients with ESRF and 695 matched controls with normal renal function. Sera were tested for anti-hantavirus IgG, using ELISA with HTNV as screening antigen. Five out of 350 cases (1.4%), and 7/695 controls (1.0%) were antibody-positive, thus resulting once again in a not statistically significant difference (p=0.48). According to a questionnaire, all antibody-positive study cases and controls had been exposed to rodents. However, the rodent HTNV reservoir *Apodemus agrarius* (the striped field mouse) is absent from Africa, hence the HTNV prototype strain 76-118 is used for its beneficial potential to give serological cross-reactions with other murine HTV pathogens, such as SEOV and Dobrava virus (DOBV), and even arvicoline HTV pathogens, such as PUUV and the newly found Tula virus (TULV) [32]. Again, none of these pathogens is present in Africa, except SEOV, due to the omnipresence of the wild rat, particularly in urban settings. The Egyptian results are in line with the low IgG seroprevalences in different African countries, previously found with the same HTNV screening agent, and presented at the first international congress of the African Association of Nephrology, held in Cairo, Egypt, in 1987 [33]. Moreover, the first pathogenic HTV isolated from a local wild rodent in Africa was SEOV: already in 1983-84, and in the WHO Collaborating Centre for Hantaviruses in Seoul, Korea, HW Lee isolated from wharf rats in Cairo two different SEOV strains, called Egypt R/12915 and Egypt R/13120, corroborating his finding of a 20.0% (499/2,499) HTNV seroprevalence in local wild wharf rats and 1.3 % (6/458) in a local asymptomatic human cohort [34]. Of note, Sangassou virus (SANGV) was isolated in 2006 from a likewise murine rodent (African wood mouse) in Guinea, West-Africa [35], and SANGV-induced human infections have been reported since, apparently without however causing a typical HFRS picture [36,37]. While SEOV-nephropathy remains a serious contender, further studies are obviously needed for pinpointing the real clinical impact of HTV's in Africa.

In summary, all here above cited studies yielded no convincing data for confirming HTV's as the culprit leading to ESRF, and prompting chronic RRT. But even if they had delivered us statistically higher prevalence than the surrounding healthy population, this would never constitute a final "proof", since observational temporal correlations do not automatically imply a causal relationship, a truth too often covered with impressive statistics in the same paper.

Intercurrent affections after a remitted HFRS episode

Since HFRS (including NE) was shown to be an acute, but transient affection in mainly young adults in previous good health, it is obvious that, once completely remitted, such patients can incur afterwards other conditions, such as arterial hypertension, arteriosclerosis, and even other nephropathies, thereby blurring the long-term follow-up results of HFRS case series. An example (IgA nephropathy) was given in section 2, and should be kept in mind, whenever a HFRS case goes on showing elevated proteinuria, hematuria, and rising levels of serum creatinine and BP. In fact, such cases are nowadays the only indication left for a renal biopsy, i.e., in the late convalescent phase. Indeed, this invasive procedure is not without risk in an already compromised patient with thrombocytopenia in the acute phase [2]. The full spectrum of clinical and laboratory anomalies of HTV infections offers the attending physician enough easy and quick check-points (e.g., presence or not of the so-called "lipid paradox"), even right after hospital admission, to postpone a renal biopsy, despite often dramatic deterioration of several renal indices such as glomerular filtration rate (GFR), and proteinuria with hematuria [1,38].

Interestingly, in 2005, Mustonen et al. noted five cases of mesangiocapillary glomerulonephritis, starting shortly after a documented but completely remitted PUUV infection. One out of these five patients progressed to ESRD, and chronic hemodialysis treatment had to be started 3 months after acute NE [39]. Miettinen et al. documented in seven other patients several forms of "post-infectious glomerulonephritis", emerging shortly after PUUV infection [40]. At the latest follow-up visit, 3/7 patients had microscopic hematuria, two had slight PU and one female had serum creatinine 114 µmol/L. Strictly spoken, these anomalies cannot be ascribed to "post-HFRS renal outcome", although a fascinating etiologic link seems evident. Indeed, our experience confirms during the acute phase of NE, the appearance, and mostly later disappearance, of several auto-immune antibodies, such as antinuclear antibodies and anticardiolipin antibodies. Such findings might misguide the attending nephrologist into an aberrant diagnostic work-up, and prompt him or her into overacting, e.g. by an early kidney biopsy for excluding lupus nephritis or ANCA-associated vasculitis. Of note, human parvovirus B19 (HPV B19) infection, well known as a cause of erythema infectiosa in children, can also rarely induce acute glomerulonephritis (endocapillary proliferative glomerulonephritis) in adults, accompanied by proteinuria (175 mg/g creatinine) and hematuria, and the advent of various autoantibodies, including antinuclear antibodies, proteinase-3-antineutrophil cytoplasmic antibodies (PR3-ANCA), anti-glomerular basement membrane (GBM) antibodies, and anticardiolipin antibodies [41]. In striking similarity with the HFRS symptoms, all these symptoms and abnormal laboratory data in this case were spontaneously self-remitting.

Arterial hypertension and/or arteriosclerosis can complicate the long-term post-HFRS course, and induce by themselves proteinuria and/ or microscopic hematuria, and ultimately declining renal function, not to be ascribed to HTV infections. Whether these sequelae could still have an effect after a highly improbable interval of more than 50 years, was examined in a total of 1,600 veterans of the Korean War (1951-54). Control subjects were selected from military units in Korea with no reported cases of HFRS. Those with HFRS had a slightly higher mortality rate (33.2%) than did non-infected individuals (32.0%), but this difference was not statistically significant. Non-Caucasian cases had significantly higher morbidity rates than did non-Caucasian controls only for transient ischemic attacks (4.8% versus 0%) and diabetes mellitus (19.3% versus 8.1%). In conclusion, HFRS did not increase mortality rates in this cohort but "might have had an impact on selected morbidity outcomes" [42].

Curiously enough, renal outcome was not a point of discussion in this large very late convalescent study after infection with the Asian HTNV.

Arterial hypertension has a too complex etiology to be detailed in this review, but was certainly not a salient feature, meaning office BP values constantly higher than 140/90 mm Hg (i.e. according to the WHO definition) in all now available long-term post-HFRS studies, see following chapter.

Current and verifiable per-and post-HFRS raw data

It is the merit of Finnish nephrologists, possessing probably the globally largest collection of electronic hospital data of hantavirus (NE) cases, to have tackled this question. Mäkelä et al. studied in 46 Finnish NE patients' renal function, proteinuria and blood pressure five years after serologically proven NE [43], whereas Miettinen et al. examined the ten-year prognosis with the same variables, in grossly the same study cohort [44]. For obvious reasons, the data collected in the study cohort of 36 patients, being exactly the same patients 5 and 10 years after the PUUV infection, is the most interesting, as presented after the 10-years study. In summary, this group showed five years after NE, instead of the expected possible amputation of renal function, an unexplained hyper filtration, with a GFR of 121 +/- 19 ml/min/1.73m^2 [44]. On the other hand, five years after NE, a slightly elevated urinary protein excretion was found, being 0.19 g/day, range 0.12-0.38. Proteinuria did not correlate with BP during the study or with the severity of AKI during the acute phase of NE. The only significant factor determining elevated proteinuria was found to be the elevated GFR (p=0.001). Even more surprising, after 10 years, the unexplained hyper filtration had disappeared, with a GFR of 113 +/- 20 ml/min/1.73m^2, and a normal proteinuria of 0.14 g/day, range 0.07-0.24. In conclusion, the 10-year prognosis of NE was considered favourable, as glomerular hyper filtration and slight proteinuria detected at 5 years disappeared during the longer follow-up [44], and despite the fact that this study cohort had after all become 10 years older. A later study on tubular proteinuria and glomerular filtration 6 years after PUUV-induced acute interstitial nephritis basically reached the same conclusions of the previous 5-year study: increased proteinuria and GFR 6 years after acute NE, the underlying mechanisms of which remained unclear however [45].

To end the discussion, the prognosis of severe AKI associated with PUUV infection was finally evaluated in a total of 556 patients hospitalized at Tampere University Hospital, Finland, from 1982 up to 2013, thereby constituting the most important retrospective study of renal outcome after a hantavirus infection. Plasma creatinine level during hospitalization, at convalescence, and one, two, and five years after acute NE, was controlled [46]. Plasma creatinine concentration was elevated (>100 µmol/L) in 459 (83%) patients. 189 patients (34%) had severe AKI defined as KDIGO stage 3, i.e. plasma creatinine ≥ 353.6 µmol/L (4.0 mg/dL) or need of dialysis during hospitalization. There were no fatality cases during the hospitalization or in the three months, following it. Control post-hospitalization plasma creatinine values were available for 188 (34%) patients. Within the first month after the acute infection, patients with severe prior AKI had higher median plasma creatinine than patients without, being 82 (range 54-184) µmol/L vs. 74 (range 55-109) µmol/L, p=0.005. After one year, median plasma creatinine concentrations were similar between patients with and without severe prior AKI, being 71 (range 36-123) µmol/L vs. 72 (range 34-116) µmol/L, p=0.711. After five years, all but one patient had normal creatinine levels. Thus, and in contrast with the worldwide well-accepted KDIGO criteria, severe AKI associated with PUUV infection is not associated with excess fatalities, and has a very good prognosis, both on short and long term [46]. As pointed out in section 2 however, HFRS, including NE, is an example of community-acquired AKI (CA-AKI), whereas most, if not all, KDIGO-based publications relate in fact to true hospital-acquired-AKI (HA-AKI) [1]. Herewith, the good renal prognosis after an acquired hantavirus infection with CA-AKI was once more confirmed, as in other Scandinavian studies [47], in contrast with some prior case-reports, suggesting the opposite [48]. For instance, a French paediatric (a 15-year-old boy) showed gradually improving renal function after a PUUV infection, finally presenting after a follow-up of more than 2 years "a creatinine clearance of about 60 ml/min/1.73 m^2". Nevertheless, this case was described in the often cited title as having "chronic renal failure" [48]. GFR rates of more than the threshold level of 60 ml/min/1.73 m^2, are not considered as having "chronic renal failure" (a fortiori not in paediatric cases), but rather having "kidney damage with mildly lowered GFR", or KDIGO stage 2 [49]. Moreover, other possible intervening causes of kidney damage, as discussed in previous chapters, had not been excluded in this case.

Finally, and according to most globally accepted KDIGO criteria, rising levels of proteinuria during an AKI insult bear a bad prognosis. Here again, cases with a hantavirus-induced AKI seem to be the noticeable exception. The type and kinetics of urine protein excretion and prognostic significance of proteinuria for the severity of AKI in acute PUUV infection was analyzed in 205 patients. The maximum 24-hour urinary protein excretion ranged from 0.14 to 17.78 g/24 h and was of nephrotic range (>3.5 g/24h) in 34% of patients, a particularity of hantavirus infections noted before [2,16,20,21,38]. Dipstick albuminuria ≥ 2+ at admission could detect 89% of the patients who subsequently developed severe AKI [50]. Nevertheless, this initial, but often massive urinary protein excretion did not appear to have any impact on the excellent prognosis, as observed in the previous 2015 Finish study.

Conclusion

In contrast to virtually all hitherto KDIGO-based studies, severe AKI during hospitalization for hantavirus infections does not lead to lasting impaired renal function, nor to an increased post-hospitalization fatality rate, even if the AKI episode is severe, and initially accompanied by massive proteinuria. So far, rare cases of hantaviral AKI, documented with successive renal biopsies, could not demonstrate a progressive inevitable course ending into ESRF, e.g. through increasing interstitial fibrosis. Consequently, it will remain hard to prove a causal link between prior hantavirus infections and currently unsolved enigma's of regional chronic kidney disease of unknown etiology (CKDu) in agricultural communities of Meso-America [51] or Sri Lanka [52].

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