Virus Research xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Virus Research

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

Hemorrhagic Fever with Renal Syndrome in the New, and Hantavirus Pulmonary Syndrome in the old world: Paradi(se)gm lost or regained?

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ARTICLE INFO

Article history:
Available online xxx

Keywords:
Hantavirus
End-stage renal disease (ESRD)
Seoul virus (SEOV)
Puumala virus (PUUV)
HFRS
HPS

ABSTRACT

Since the first clinical description in 1994 of the so-called "Hantavirus Pulmonary Syndrome" (HPS) as a "newly recognized disease", hantavirus infections have always been characterized as presenting in two distinct syndromes, the so-called "Hemorrhagic Fever with Renal Syndrome" (HFRS) in the Old World, with the kidney as main target organ, in contrast to HPS in the New World, with the lung as main target organ. However, European literature mentions already since 1934 a mostly milder local HFRS form, aptly named "nephropathia epidemica" (NE), and caused by the prototype European hantavirus species *Puumala virus* (PUUV). Several NE reports dating from the 1980s and early 1990s described already non-cardiogenic HPS-like lung involvement, prior to any kidney involvement, and increasing evidence is now mounting that a considerable clinical overlap exists between HPS and HFRS. Moreover, growing immunologic insights point to common pathologic mechanisms, leading to capillary hyperpermeability, the cardinal feature of all hantavirus infections, both of the New and Old World. It is now perhaps time to reconsider the paradigm of two "different" syndromes caused by viruses of the same *Hantavirus* genus in the same *Bunyaviridae* family, and to agree on a common, more logical disease denomination, such as simply and briefly "Hantavirus fever".

Since the first description in 1994 of HPS induced by *Sin Nombre virus* (SNV) (Duchin et al., 1994), followed in 1996 by Andes virus (ANDV) and later several other SNV- or ANDV-like agents, world literature perpetually mentions a distinct transatlantic dichotomy between New world hantavirus clinical presentation coined as "HPS (or HCPS)", versus Old World clinical presentation as "HFRS". The latter is characterized by often massive, but always transient proteinuria, and varying degrees of what is now preferentially called "acute kidney injury" (AKI), instead of the former "acute renal failure" (ARF). HPS comprises as cardinal symptom a peculiar form of "acute lung injury" (ALI), which, together with heart failure, can be life-threatening. Both HPS and HFRS have in common fever, myalgiae, abdominal discomfort, thrombocytopenia, and a series of other lab anomalies, amongst which elevated levels of CRP and/or LDH. When it is clear that (A) these SNV and ANDV pathogens were now almost 20 years ago truly "newly discovered", (B) that the deer mouse (*Peromyscus maniculatus*), respectively the long-tailed rice rat (*Oligoryzomys longicaudatus*) were then "newly discovered" as their rodent carriers, and (C) that the then used RT-PCR was a historical breakthrough for quick genetic characterization of new hantaviruses, it remains nevertheless highly questionable if the described clinical presentation of HPS was truly (we quote) "a newly recognized disease" (Duchin et al., 1994). "Newly recognized" could mean the clinical picture had never been described in American literature until 1994, but the question remains if that was also the case for European, Russian, Korean and Chinese literature until 1994? This sudden 1994 paradigm that genetically closely related viruses would generate in humans a totally different clinical picture is all but obvious, the more so since all pathogenic hantaviruses have the same entry mechanism in humans, both in HFRS as in HPS, via beta 3 integrin receptors in the lower respiratory tract, producing after entry more or less the same array of pro-inflammatory cytokines (Maes et al., 2004; Terajima and Ennis, 2011). Moreover, the human host's immune response (the "cytokine storm") is now recognized as the main pathogenic determinant, not so much the virus itself, which is notorious for its absence of visible cytopathic effects (CPE) (Maes et al., 2004). Endothelial dysfunction, with ensuing but temporary capillary hyperpermeability, is now generally accepted as the common pathway to both HPS and HFRS (Terajima and Ennis, 2011).

Moreover, the divide between the New and Old World is not so deep as it appears at first sight. The often-read introduction in virtually each hantavirus paper that the first detection, respectively first isolation of a New World hantaviral pathogen took place in 1993, is historically untrue, and skips more than a decade of spearhead American pioneer research on hantaviruses and

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http://dx.doi.org/10.1016/j.virusres.2013.12.036

their involved rodent reservoirs. Indeed, the first (1982) American rodents demonstrated, even with highly specific plaque reduction neutralization tests (PRNT), to be hantavirus-positive, were no sigmodontine nor neotomine, but in fact murine rodents, namely wild wharf rats or *Norway rats* (*Rattus norvegicus*), i.e. the only cosmopolitan rodent species, historically originating from the Old World. The first hantavirus-positive rats were found in Philadelphia, PA, and in Houston, TX (No authors listed, NEJM 1982). The first (1984) pathogenic hantavirus isolated in the New World was a *Seoul virus* (SEOV) from a wild rat caught in Philadelphia, and called the *Girard Point virus* (LeDuc et al., 1984). Further SEOV isolations followed in 1985 from feral rats (*Rattus norvegicus*), caught in New Orleans (*Tchoupitoulas virus*) (Tsai et al., 1985), in Brazil (*Belem virus*) (LeDuc et al., 1985), and in 1987 in Baltimore, MD (*Baltimore rat virus*) (Childs et al., 1987). Thus, eight representative hantavirus isolates from the New World and from Asia known at that moment appeared then to represent a new and unique group and a separate genus in the *Bunyaviridae* family, with however a conspicuous absence of human pathogenicity in the New World (Schmaljohn et al., 1985), since so-called SEOV nephropathy (a particular form of HFRS) had been described at that moment only in the Far East. However, only three years later (1988), unmistakable proof of SEOV infection in some Baltimore asymptomatic individuals with life-long residence in Baltimore and an absence of foreign travel, proved that in the Americas, as in Eurasia, subclinical hantavirus infections existed (Childs et al., 1988). When admittedly in the Americas SEOV does not cause big epidemics like in China, isolated HFRS cases almost certainly go nowadays unrecognized or are misdiagnosed, even in the best hands, as proven in 2007 by a clear NE case in a patient coming from Europe: despite suggestive clinics, typical lab anomalies, and even a kidney biopsy, a double concomitant but contradicting nephrological affliction was tentatively proposed in a renowned American clinical series (Rabb and Colvin, 2007), instead of relying on simple hantavirus serology, as later proposed in a Correspondence Letter (Haas et al., 2008).

Of note, the first published account of symptomatic (fever, AKI and thrombocytopenia) and seroproven hantavirus infections in the Americas (Brazil) were HFRS, not HPS, cases, originally suspected of leptospirosis (Hinrichsen et al., 1993), mainly another rat-transmitted disease. Moreover, three domestic HFRS cases of PRNT-proven SEOV (*Baltimore rat virus*) nephropathy in the USA were eventually, and after a long shelf-life, published a few weeks before the earliest HPS description (Glass et al., 1994), but were apparently later forgotten in literature. The fourth case is however a recent and well-documented domestic case of SEOV nephropathy, again in Maryland, in a patient with no known exposure to rats, which had never traveled abroad, and with a negative rodent capture action around his home (Woods et al., 2009). This publication wrongly claims to be the first such domestic case-report in the USA, but is indeed the first SEOV case confirmed in the New World with positive RT-PCR in the acute phase. The message is therefore even reinforced: symptomatic (this last case required 6 dialysis sessions) human SEOV infection is proven in the USA, hence HFRS is really present in the New World, and everybody is potentially at risk. Of note, SEOV infections can also cause primarily liver instead of kidney involvement, thus mimicking unclassifiable viral hepatitis, or serious hepatic complications such as acute fatty liver of pregnancy (AFLP) syndrome, and the hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome during pregnancy (Macé et al., 2013). If such atypical SEOV infections are globally and timely diagnosed, dramatic interventions, amongst which urgent salvage delivery and/or unnecessary liver or kidney biopsies, can be avoided (Clement et al., 2013a). It remains baffling for the clinician however that such primordial liver problems should indefinitely be coined as "HFRS", and for the epidemiologist that its occurrence should not even be suspected in the New World.

A curious incongruity in American HFRS assessment, is the saga now going on for 20 years of what should be called "subclinical chronic Baltimore rat virus SEOV nephropathy", being continuously cited as a putative cause of hypertensive end-stage renal disease (ESRD) (Glass et al., 1993). This so-called consistent relationship between SEOV infection and hypertensive renal disease, and even hypertensive ESRD, is based solely on asymptomatic SEOV-seropositivity in only 7 out of 254 Baltimore chronic dialysis patients, all African-Americans, 71% (5/7) being older than 60 years. This 1993 retrospective observational study contained no prior disease history, no prior nephrological work-out, nor documented prior follow-up of renal function, blood pressure or proteinuria to illustrate the years-long slow decline to ESRD. The only assessment was a hantavirus serology when the patients were already on chronic dialysis, i.e. at the final stage of each form of renal disease, whereby each assumption concerning the original renal problem, starting often more than a decade before, becomes extremely dubious. Moreover, observational associations (in this case: SEOV seropositivity and hypertensive ESRD) cannot confirm casuality, even less when supported by only a few patients. Conversely, in China, where tens of thousands of overt SEOV cases were registered so far, no evidence of such harm was ever found since the 1950s. Indeed, a grand total of over 1.4 million Chinese HFRS cases have been reported from the 10950s up to 2010, with over 46,000 registered deaths. The record year was 1986, with 115,985 confirmed cases, and 2561 (2.2%) deaths (Liu et al., 2011). These Chinese epidemics were and are mostly a mixture of SEOV and *Hantaan virus* (HTNV) HFRS, but arterial hypertension, and even less hypertensive ESRD, was never mentioned as a national health problem in China, caused by no matter which hantavirus infection. If in contrast HFRS is said to be absent indeed in the New World, how then to maintain that an asymptomatic HFRS infection could explain potentially thousands of cases of hypertensive ESRD locally in that same New World?

In Europe and European Russia, an ever underestimated total of now more than 225,000 registered HFRS cases, mostly induced by PUUV, were registered so far, 75% of which in European Russia (Clement et al., 2013b). For instance, only in the 1978–1992 period, a total of 65,906 cases had already been registered in the European part of Russia. In some peak years, Russia witnessed more than 10,000 cases/year, e.g. 11,413 in 1985 (WHO, 1993). Registered HFRS numbers in Western Europe also show recently epidemic proportions (e.g. 3259 cases in Finland, 2008, and 2824 cases in Germany, 2012), probably as a result of global warming (Clement et al., 2009; Makary et al., 2010; Krüger et al., 2013). Only between 1995 and 2008, Finland registered already 22,681 NE cases, resulting in 50,129 hospital days (Makary et al., 2010). Finland, the most endemic country in the world for hantavirus infections, has no national health problem of hypertensive ESRD.

In the Americas, the total of HPS cases registered in almost 20 years, reaches now up to 2,500, albeit admittedly with a much higher fatality rate of still 35%. In comparison, fatality rate for NE in Finland is now only 0.08%, versus 2.1% for HFRS in China (Clement et al., 2013b). However, clinical experience with NE existed in Europe, and first in Sweden, since 1934, i.e. 60 years before the discovery of HPS. The adjective "epidemica" says enough, meaning that some local clinicians saw and still see dozens of NE cases per year. Moreover, comparing NE incidence (recorded over 14 years) with IFA IgG PUUV-antibody prevalence in a highly endemic area of Sweden, this prevalence rate in the oldest age groups (>60 years) appeared to be 14–20 times higher than the accumulated life-risk of once being hospitalized with NE for men and women, respectively. This observation proves that the vast majority of PUUV infections and their transient renal involvement passes unnoticed, or is interpreted as a 'bad flu' (Niklasson et al., 1987). Consequently, it can be assumed that Russian and European authors

Please cite this article in press as: Clement, J., et al., Hemorrhagic Fever with Renal Syndrome in the New, and Hantavirus Pulmonary Syndrome in the old world: Paradi(se)gm lost or regained? Virus Res. (2014), http://dx.doi.org/10.1016/j.virusres.2013.12.036