Beechnuts and outbreaks of nephropathia epidemica (NE): of mast, mice and men

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Introduction, Definitions and Forgotten Facts

Hantaviruses are ‘emerging’ viruses and the only viral haemorrhagic fever agents with a worldwide distribution, including the temperate Northern hemisphere. They are spread by wild rodents (and perhaps also insectivores), infecting man via their aerosolized but infectious excreta. So far, at least 22 different hantavirus species are officially recognized (1), each with its own main rodent reservoir and hence specific geographical presence (2). The most important pathogens are Hantaan and Seoul virus in Asia, Puumala and Dobrava virus in Europe, and Sin Nombre and Andes virus in the Americas. The American hantaviruses, discovered only in 1993, affect mainly the human lung and cause the ‘hantavirus cardiopulmonary syndrome’ (HCPS), with a current fatality rate of ~30% (2). In contrast, all Old World hantaviruses are targeted mainly to the human kidney resulting in the ‘haemorrhagic fever with renal syndrome’ (HFRS), an often epidemic form of acute kidney injury (AKI), characterized by interstitial haemorrhagic nephritis and sometimes acute tubular necrosis. Still, HCPs and HFRS considerably overlap: both ‘syndromes’ are rarely complete; the ‘haemorrhagic’ component is lacking in many HFRS and in virtually all HCPS cases (2–4). In fact, HFRS and HCPS are misnomers. Of note, massive but transient proteinuria, the quintessential presenting symptom in HFRS, is also found in 100% of the so-called HCPS cases, some of which may actually need acute dialysis as a treatment (4). Thus, as J. Desmyter proposed already in 1984, a general denomination such as ‘Hantavirus disease’ is shorter, less misleading, and more acceptable to clinicians, virologists and epidemiologists alike [5].

Among hantavirus pathogens, Puumala virus (PUUV) is the least severe. It causes a condition aptly named ‘nephropathia epidemica’ (NE) since its first description in 1934 in Sweden [6]. The reservoir and vector for PUUV is the bank vole (Myodes glareolus), one of the most common wild rodents in Europe and Western Russia. With the advent of RT–PCR and subsequent sequencing, virus identification both in man and rodent, and even its geographic localization became possible, with a clear regional clustering of the different PUUV species [7,8] (Figure 1). It is noteworthy that genetically related PUUV species from Japan, Korea and China have been isolated from vole species other than the European M. glareolus, but showed, so far, no known pathogenicity. Overall, NE remains an epidemic (or sporadic) kidney disease prevalent west of the Ural Mountains. Bank voles thrive in a ‘wet habitat’ [9]. So, their preferred biotope is the temperate forests of Western and Central Europe, or the boreal forests (taiga) in Northern Europe. This simple but often overlooked fact explains why NE is virtually absent from most of the south of Europe, whose predominant biotope, the ‘Mediterranean shrub’, is much drier. Outside of Fennoscandia, Western Europe and the Balkans are clearly more endemic than all Central European countries, whereas big Eastern European countries, such as Poland, Belarus and Ukraine, have so far reported only a few or no cases at all; this also explains why no PUUV species have been characterized from these regions (Figure 1).

NE symptoms consist of sudden fever, myalgia often associated to severe lumbalgia (due to interstitial oedematous renal swelling), and a rapidly progressive but ultimately self-remitting acute renal failure (ARF). Early signs include thrombocytopenia and proteinuria, which may be marked, but both of which always resolve spontaneously. NE and HFRS, in general, are the great imitators of leptospirosis, another (mostly) rodent-borne zoonosis with a worldwide spread [2,4]. There are no distinctive NE features in symptoms, in lab anomalies or even on...
kidney biopsy [4,10,11]. Hypokalaemia is a rare feature of (even severe) ARF but can be seen in both conditions [4,8]. Even epidemiologic presentation can be exactly the same, e.g. outbreaks after floods [2,4]. The only pathognomonic clinical sign is early-onset acute myopia, present in ∼25% of NE cases but absent in leptospirosis [4,10,11]. Thus, confirmation of a clinical suspicion of NE or leptospirosis (which can even occur concomitantly) should always rely on serology and/or PCR [2,4,7,8].

However, only 13% of all PUUV infections are serodiagnosed, the other being interpreted as ‘a bad flu’ [4,12] or remaining unnoticed. HFRS, including NE, is now the most underestimated cause of infectious ARF worldwide. In Russia alone, 68 612 HFRS cases, most of which NE, were registered (i.e. often hospitalized) between 1978 and 1992. They peaked in 1985 with 11 413 cases and a fatality rate of 8% [13]. The reasons for this high mortality remain unclear but might be linked to more ‘severe’ PUUV serotypes present in Russia. Clinical course in Sweden, compared to Russia, revealed more severe and fatal cases of the latter [14], and acute perinephric haemorrhage, a life-threatening complication, has been reported only from Russia so far [15].

By coincidence, the same 1993 World Health Organization (WHO) report [13] about the Russian NE data also announced the seven very first American HCPS cases, catching worldwide attention ever since, despite the persistence of largely ignored thousands of hantavirus cases each year in Russia. The current indiffERENCE for the prevalence of HFRS in the Far East is even more unwarranted: in China alone, an astonishing number of 1 256 431 HFRS cases with 44 304 (3.53%) registered deaths were reported between 1950 and 1997 [16]; 1986 was the record year with 115 985 confirmed cases and 2 561 (2.2%) deaths [17]. For comparison, between 1993 and 2009, only 506 confirmed cases of HCPS were registered in the USA, and ∼2 500 cases in the entire Americas [18]. European figures (see below) are much more modest, with a fatality rate of only 0.1%. Still, neither NE nor HFRS are specifically listed so far in the ERA–EDTA Registry, despite the yearly registration of six other causes of intermittent nephritis [19]. This omission may be due to the fact that HFRS rarely, if ever, leads to end-stage renal failure, contradicting a rare American study suggesting the opposite [20].

**NE Rise in Fennoscandia**

With ∼1000 NE cases per year, Finland has reported, between 1979 and 2008, >70% of all cases registered within Europe. However, an increasing trend was noted in the last decade, with peaks of 2 300 cases in 1999, 2 603 in 2002, 2 526 in 2005 [21] and, an all-time high, 3 259 cases in 2008 [22]. With its population of 5.2 million, the 2008 incidence reached 62.6/105, the highest in the world. NE is thus by far the most important cause of infectious ARF in Finland, as it probably is in the rest of Europe. It prompted acute dialysis therapy in 5%, but resulted in a fatality rate of only 0.07% [12]. Remarkably, for an AKI diagnosis, family clustering is observed in 8% of cases [12]. In Sweden, NE has been registered from 1989 onwards. Incidence averaged between 200 and 400 per year, but peaked suddenly to 2 195 in 2007, and again to 1 483 in 2008 [23]. In Norway, ∼50 cases occur annually, peaking to 239 in 1998 [12]. Winter NE peaks are characteristic for Fennoscandia, in contrast with the summer peaks in Western Europe [22,23]. Global warming during wintertime has been incriminated somewhat paradoxically for an increased contact between humans and voles, since the decreased protective snow cover in Fennoscandia is supposed to favour bank voles’ entry into human dwellings, in search for food and shelter [23]. The vegetation type that covers most of Norway, Sweden and Finland is another difference, since the boreal forest or taiga consists mainly of pine trees, in contrast to the temperate forest in the rest of Europe, wherein deciduous broadleaf trees predominate. Overall, the 3-yearly NE peaks in Fennoscandia are ascribed to predator–prey cycles, a mechanism very different from the one operative in temperate Europe [23].

**Belgium and the Predictive Power of Beechnuts**

In Belgium, between 1983 and 2009, a total of 2 573 NE cases were reported [4,24] (Figure 2). This 27-year observation period, exceptionally long for an emerging infection, is explained by the long-standing interest for hantaviruses in the country. A first clinical description of what was later confirmed as a Brussels laboratory HFRS outbreak was already reported in 1979 [10]. The presence of a PUUV-like antigen in Belgian bank voles [25], the earliest clinical description of three NE cases [26], and a first seroepidemiological study were all published in 1983 [27]. The serodiagnosis of NE was improved by the isolation in Belgium and in 1983 of a Russian PUUV strain, CG 18–20 [28]. It allowed the seroconfirmation of early Belgian NE cases and of the first autochthonous German case in 1985 [29]. The autochthonous Belgian PUUV strains CG 13891, CG 14444 and CG 14445 were isolated in 1985 [8,30] (Figure 1). Native or recombinant versions of CG 13891 were later successfully used by the national hantavirus reference laboratory in Belgium, and form now the base for serodiagnosis in France [31–33]. Recurrent NE peaks were noted from 1990 onwards in both countries, first with 3-year and then with 2-year intervals (Figure 2). They could not be attributed to the fluctuating degrees of medical awareness or seromonitoring, even with performing more diagnostic tests. An underlying ecological mechanism, dependent mainly on climate factors, was thus first postulated in 2005 [34] and recently confirmed [24]; the so-called ‘mast phenomenon’. The seeds of deciduous broadleaf trees, such as oaks but predominantly beeches, are commonly called ‘mast’ and constitute the staple food source for voles. It was hypothesized that a higher food supply in autumn promotes a better winter survival and earlier spring breeding in voles, leading to rodent densities up to 20 times the norm. Interestingly, for many years, a positive correlation had been found between rodent density and prevalence of hantavirus infection, both in Old and New World rodent reservoirs [9,18,23]. Older males showed a higher degree of infection and more bite wounds [9,18]. This suggests a mainly horizontal intraspecies
transmission of hantavirus, occurring during fighting in the mating season, with a density-dependent enhancement. Finally, increased single-species density often means lower local biodiversity of other rodent species, which in turn ultimately may lead to exponential increase of hantavirus infection, by a mechanism recently called ‘zoonotic release’ [18]. In this ‘mast hypothesis’, beeches seem far more operative than oaks and other broadleaf trees, since in contrast to the latter, the spread of the European beech (Fagus sylvatica) is almost identical to the spread of NE in Europe [35] (Figure 3).

A recent similar study, relying on the same Belgian 1995–2007 NE registry but using quantitative mast data, came independently to exactly the same conclusions: NE outbreaks are correlated with heavy masting and high autumn temperatures 1 year before and high summer temperatures 2 years before NE peaks [36]. Moreover, heavy autumn mast production precedes each major NE peak, particularly so in 2004 and to a lesser degree in 2007 [24,36] (Figure 2).

One study also showed a strong correlation with cold and moist summers and NE peaks 3 years later. The correlation improved when only July was selected as the most representative summer month [24]. Thus, the summer of 2003, estimated to be the hottest since 1540 in Europe (mean temperature in Belgium 19.7°C, normal 17°C) (Figure 2), stimulated flower bud initiation in oaks and even more in beeches, thus paving the way via particularly heavy mast production in autumn 2004 for the most important NE outbreak observed until then, not only in Belgium, but also in France and Germany, with an unprecedented total of 1073 registered cases in the three countries in 2005 (Figure 2): a rare example of tree ecology having an impact on a kidney disease [24,36]. Clearly, the increasing NE incidences in Belgium during recent years may be considered as a consequence of global warming, as it is apparently also the case in its neighbouring countries.

**NE Patterns in France and Germany**

The first NE case, published in France in 1983 [37], initiated an observation period as long as that in Belgium.

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**Fig. 1.** Neighbour-joining phylogenetic tree based on full-length nucleocapsid protein sequences of Puumala virus strains found in GenBank (up to June 2009) with bootstrap analysis based on 10 000 replicates to estimate the statistical support for the branching pattern. The scale bar indicates an evolutionary distance of 0.02 substitutions per position in the sequence. Sotkamo from Finland is the reference European strain. CG 1820 (isolated in 1983) and CG 13891, CG 14444, and CG 14445 (isolated in 1985) were used for serodiagnosis of early Western European NE cases from the early 1980s onwards. Umea/hu and Heidelberg/hu are human isolates; all others are rodent isolates. Note the clear geographic clustering.

**Fig. 2.** Annual seroconfirmed NE cases in Belgium (first white bars), Germany (middle light grey bars, from 2001 onwards) and France (last dark grey bars) 1983–2009. These figures represent probably only ~13% of real PUUV infections (see text). The 76 first Franco-Belgian 1977–86 cases [11] are not included, since annual distribution was not available. The mean Belgian temperatures for summer (June–July–August) (bold line) and autumn (September–October–November) (dotted line) are also given. Note the peak for summer temperatures in 2003 and for autumn in 2006 (see text). These Belgian temperature data are only indicative for some regions of adjacent Germany and Northern France. Belgian mast years are marked with full arrows. Since 1992, each mast year is followed the next year by a NE peak in Belgium and France. Moreover, mast years augmented from a 3-year to a 2-year cyclicity. The year 2006 was a beech mast year particularly in Germany (marked as a grey arrow with asterisk), followed by a record high number of German NE cases. The jigsaw pattern of higher summer temperatures since 1995 is mirrored by a jigsaw NE peak pattern in Belgium and France, often with a 2-year lag. The recent epidemic trend of NE in all three countries is underscored by the stark upwards trend of autumn temperatures (dotted line), particularly since 2004.
A total of 1,736 cases were reported in 25 years (1983–2007) with yearly fluctuations surprisingly similar to those in the neighbouring Belgium (Figure 2). Of note, also the same screening antigen, CG 13891, was commonly used since 1989 [31–33]. Not surprisingly, NE is endemic only in the northeast of France, the region with the highest beech forest cover, particularly so in the region Champagne–Ardennes. So far, only one RT–PCR-confirmed PUUV case has been demonstrated in Southern France, around Perpignan (Pyrénées–Orientales department), where bank voles prefer the cooler and wetter environment of the mountains [7]. Why French NE figures are conspicuously lower from 2006 onwards (Figure 2) remains unclear. At least for 2007, they correspond to a much lower than expected number of locally captured bank voles, all of which were PUUV-negative [39].

The Western European 2005 record almost doubled in 2007 (total 2,112 cases), exclusively as a result of the input of Germany, which witnessed that year an extraordinary 1,689 cases (Figure 2) [40]. Germany started an official registry for hantavirus infections only in 2001 and reported in this 8-year period (2001–08) 3,062 cases or 2.04 times more than in Belgium for the same period (1,499 cases), but with the same rising trend. Two-thirds of all German NE cases are localized in Baden–Württemberg (Southwest Germany). The endemic NE in this state is now the highest in Western Europe. Its population (10.7 million) is comparable to that of Belgium (10.3 million), but the beech coverage is much higher (Figure 3). In this German state, 2007 NE incidence was 3.6 times higher (10.1/10^5) than the record 2005 incidence (2.8/10^5) for Belgium [41,42]. It is striking that, in this same state, districts with the highest beech forest cover (15% or more) correlate significantly with the highest district NE incidences (50/10^5). Moreover, for each 5% increase in beech coverage per district, risk for NE almost doubled [42]. The first recorded (February...
1990) NE outbreak in Germany, with 24 immunoglobulin M (IgM)-positive cases within 2 weeks, occurred also in this state, curiously enough not in the local population but in American military bivouacking for a winter exercise in a vole-infested terrain near the city of Ulm [43]. This outbreak illustrates that the greatest risk factor for NE is and remains human exposure to PUUV, particularly if it occurs in an unusual form (winter camping). It is noteworthy that the earliest (January 1984) clinical description, including a kidney biopsy, of a seroconfirmed NE case in Germany was also in a Belgian military, likewise infected during winter exercises, this time around Spich (North Rhine-Westphalia) [44]. The serum V84-58 of this pioneer ‘German’ case served to characterize the prototype Western European PUUV strain CG 13891 [30]. In Baden–Württemberg, the absolute record year 2007 (1689 cases) was preceded by heavy beech masting in autumn 2006, the mildest winter ever recorded in Germany, a very warm spring 2007, and a noticeable increase in bank vole population [41]. The PUUV prevalence reached up to 76% in bank voles captured during the 2007 outbreak [40]. Most years are simultaneous in most countries of Western Europe, including even the British Isles [45], but exceptions can occur due to regional differences. Indeed, neither Belgium nor France has witnessed extraordinary masting in 2006 (Figure 2). The fact, however, that Belgium witnessed in 2007 its third highest NE peak (298 cases), even without prior heavy masting, can be explained by the preceding warmest autumn ever noted (mean temperature: 13.9°C, normal 10.4°C), followed by the mildest winter ever recorded in Belgium (mean 6.6°C, normal 3.1°C) [24,36]. A 7-year (2001–07) NE risk factor study in Baden–Württemberg concluded that a combination of a mild winter and prior heavy masting constitutes the greatest risk, an excellent supply of beechnuts conferring by itself already a risk ratio of 2.86 (95% confidence interval 1.81–4.50) [42].

Conclusion

In summary, a warm autumn and winter 1 year before, a hot summer (particularly July) 2 years before, and a cold and moist summer (particularly July) 3 years before could serve as early warning indicators for potential NE outbreaks in Western Europe, particularly if a heavy beech crop is observed together with a warm autumn 1 year before [24,36]. If global warming with ever hotter summers and very mild autumns plus winters are to be expected for the next years, further NE epidemics can be anticipated, although regional differences can persist, as shown in France and Germany. Satellite observations, monitoring several indices of vegetation in broadleaf forests, are now checking these correlations in the past and present (Working Group for Interdisciplinary Research, Faculties of Bio-engineering and Medicine, Katholieke Universiteit of Leuven, Belgium) [46]. Thus, counting (beech)nuts in the Ardennes, as in other broadleaf forests of Western Europe, can bear strategic implications. When general McAuliffe during the 1944–45 ‘battle of the bulge’ in the heart of the Belgian Ardennes pronounced his famous ‘Nuts!’ as an answer to operation ‘Herbstnebel’, he probably meant something else.

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References

Kidney allocation: where utility and fairness meet

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Transplantation is the preferred treatment option for end-stage renal disease because it offers a survival advantage over dialysis for the majority of patients [1]. Renal transplantation is saving, as well as improving, lives, but the benefits may differ among groups. Unfortunately, due to the static supply of donor organs (Figure 1, left), the disparity with the increasing numbers of patients placed on the waiting list and therewith waiting times continues to increase. The median waiting time for a deceased donor


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