

医薬品 研究報告 調査報告書

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販売名(企業名)		合成血「日赤」(日本赤十字社) 照射合成血「日赤」(日本赤十字社)			スウェーデン	
研究報告の概要	<p>○スウェーデンのPuumalaウイルス感染アウトブレイク ハンタウイルスの一種Puumalaウイルスは、スウェーデン、フィンランド、ノルウェー、ロシア、中央ヨーロッパの一部に土着しており、自然宿主であるハタネズミの排泄物からヒトに感染する。スウェーデンにおけるPuumalaウイルスの予期せぬ大規模アウトブレイクにより、2007年のVästerbotten地方の流行性腎症患者の数は100,000人当り313人に至った。齧歯類の増加の他、気候温暖化および地表を覆う積雪の減少により、ウイルスを媒介するハタネズミの活動が活発だったことが、当該アウトブレイクの一因であろうと考えられる。</p>					使用上の注意記載状況・ その他参考事項等
						合成血「日赤」 照射合成血「日赤」 血液を介するウイルス、 細菌、原虫等の感染 vCJD等の伝播のリスク
報告企業の意見			今後の対応			
スウェーデンにおいてPuumalaウイルスの大規模アウトブレイクが発生し、2007年Västerbotten地方の流行性腎症患者の数は100,000人当り313人に至ったとの報告である。			日本赤十字社では、輸血感染症対策として問診時に海外渡航歴の有無を確認し、帰国(入国)後4週間は献血不適としている。今後も引き続き、新興・再興感染症の発生状況等に関する情報の収集に努める。			



Outbreak of Puumala Virus Infection, Sweden

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An unexpected and large outbreak of Puumala virus infection in Sweden resulted in 313 nephropathia epidemica patients/100,000 persons in Västerbotten County during 2007. An increase in the rodent population, milder weather, and less snow cover probably contributed to the outbreak.

Members of the genus *Hantavirus* (family *Bunyaviridae*) are rodent-borne pathogens, and virus is transmitted to humans by inhalation of infected rodent excreta (1). In Sweden, Finland, Norway, Russia, and parts of central Europe, Puumala virus (PUUV) is endemic in bank voles (*Myodes glareolus*). PUUV infection in humans cause nephropathia epidemica (NE), a mild form of hemorrhagic fever with renal syndrome (HFRS). In Sweden ≈90% of all NE cases are found in the 4 northernmost counties. Västerbotten County (Figure 1) has the highest incidence of human hantavirus infection in Sweden and probably one of the highest worldwide. Historically, the incidence rate is 20 per 100,000 persons per year (2), but the true incidence is considered to be 7–8 times higher (3).

There is a 3–4-year periodicity in the number of NE cases that is linked to the bank vole population dynamics in northern Sweden (2). After inhaling infectious aerosols originating from rodent saliva, urine, or feces, the patient has a 1–5-week incubation period before onset of disease symptoms. The most common NE symptoms are fever, headache, nausea, abdominal and back pain, vomiting, myalgia, and visual disturbance. One third of the patients have mostly mild hemorrhagic manifestations (4,5). Renal failure is typical with initial oliguria during the acute phase and polyuria in the convalescence phase. Dialysis is sometimes needed and <0.5% of NE cases are fatal. There is no effective treatment or available vaccine.

The Study

The local University Hospital of Umeå is the reference center for diagnosis of NE serving the 4 northernmost counties of Sweden, and many patients with NE are hospitalized here. In 2007, a sudden and large outbreak of hantavirus infections occurred in northern Sweden. The outbreak peaked in January 2007 (Figure 1) with many NE patients who had a considerable effect on public health services.

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The NE outbreak continued in the following months, but with fewer cases than in early 2007 (Figure 1).

For NE diagnosis, we used an immunofluorescence assay to detect PUUV-reactive immunoglobulin (Ig) M and IgG antibodies in serum of all patients with clinically suspected NE (6). A real-time reverse transcription-PCR (6) was used to obtain an amplification product from 1 patient sample. This product was sequenced and the S-segment sequence obtained (GenBank accession no. EU177630) was highly homologous to those of other rodent PUUV isolates from the area.

NE is a reportable disease under the Swedish Communicable Diseases Act. The outbreak peaked during the first 3 months of 2007; 972 cases were recorded in Sweden and 474 cases in Västerbotten County. NE patients mostly showed classic HFRS symptoms and mild to severe disease requiring hospitalization and occasionally intensive care. Accordingly, as many as 30% of the patients whose conditions had been diagnosed as NE were hospitalized, and 2 known deaths (case-fatality rate 0.25%) in the 2 northernmost counties in Sweden were recorded during the first 3 months of 2007. No patient had to continue dialysis after the acute phase of the disease.

We detected PUUV RNA in the milk of 2 breastfeeding women with a diagnosis of NE. Their children did not show any clinical symptoms of NE. However, we did not have access to samples to analyze whether the children had asymptomatic infections. Three pregnant women also had received a diagnosis of NE, but no clinical evidence of transmission from mother to child was reported. Analyses of the placentas did not detect any PUUV RNA. Only maternal IgG antibodies to PUUV were found in blood from umbilical cords. One woman miscarried after 12 weeks of pregnancy 3 weeks before showing symptoms of clinical NE, and death of the fetus may have been caused by viremia during the incubation period. During the peak of the outbreak (December 2006–March 2007), 488 cases occurred in Västerbotten County, and, as expected, more men (58%, 281/488) than women (42%, 207/488) had NE; most cases (72%) were among persons 35–74 years of age (Table).

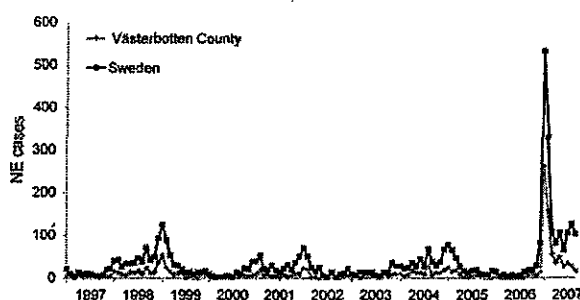


Figure 1. Monthly incidence of nephropathia epidemica (NE) in Sweden and Västerbotten County, Sweden, January 1997–September 2007.

The incidence of NE in Västerbotten County was 313 diagnosed cases/100,000 persons in 2007 compared with 73/100,000 in 1999, 38/100,000 in 2002, and 61/100,000 in 2005 (Figure 1). The number of NE cases usually depends on the size of the vole population, which peaks every third to fourth year (2,7). An increase in the bank vole population was reported in northern Sweden in the fall of 2006, with a trap index of 7.64. This index is similar to those of 2 NE peaks in the fall of 1998–1999 and 2004–2005 when trap indices were ≈ 8 (8). Trapping indices represents the number of voles captured per 100 trapping nights, a reflection of the relative population size on each sampling occasion (9). Thus, the bank vole population was high, but not more than in previous peak years and could not explain the high number of NE cases in 2007.

We considered other possible factors influencing hantavirus transmission to humans. One factor is increased exposure of humans to infected rodent excreta. We had received several reports from inhabitants in areas where bank voles normally live that more bank voles were found in traps inside houses than usual. When we investigated the weather conditions during this period, December 2006 was exceptional with respect to the mild weather with no or little snow and hard ice cover in the coastal area of northern Sweden. In Västerbotten County, the average temperature in December was 6.0°C–9.0°C warmer than normal (normally the average temperature in Västerbotten County varies by –4°C along the coast and –13°C in the mountains). The average temperature in Sweden was 4.5°C–9.5°C warmer than normal in December 2006 (Figure 2). The snow cover during winter is important for bank vole survival because bank voles have access to food below the snow and hide from predators and the cold (10). During 2 previous NE peak periods (2001–2002 and 2004–2005), the ground was already covered with snow in early winter (Figure 2). For these reasons, during December 2006, when the ground had no snow cover for 25 of 31 days (Figure 2), bank voles may have sought refuge in barns and houses and other buildings, thereby increasing the exposure for the human population at risk. A concurrent epizootic may have occurred among bank voles, which resulted in larger

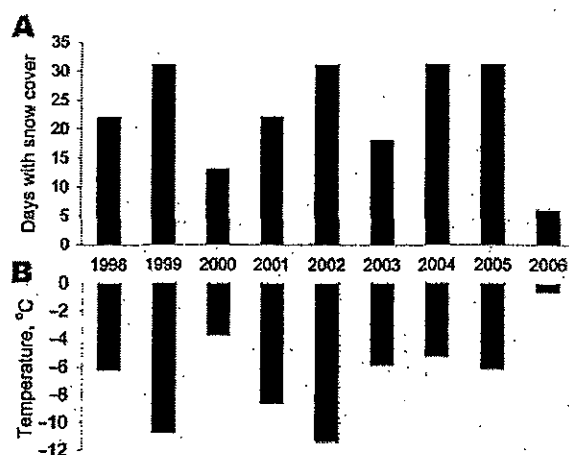


Figure 2. Climate conditions, December 1998–2006, in the nephropathia epidemica outbreak area of Västerbotten County, Sweden. A) Number of days with a snow cover. B) Average temperature. Snow cover was defined as a snow depth >0 cm. Measurements were made in locations ≈ 30 km from the coast. Data were obtained from the Swedish Meteorological and Hydrological Institute.

numbers of infectious animals, as shown in previous rodent studies (11,12). However, we did not have access to rodents during this period and this hypothesis needs to be studied.

Conclusions

This report shows how a zoonotic disease can suddenly result in an unexpected and large human outbreak. Presently, the numbers of NE cases in northern Sweden are still unusually high. Data indicate that the bank vole population during the fall of 2007 increased to an even higher level and a new outbreak is forecasted (8). However, the size of the rodent population is not the only factor that determines the size of a hantavirus epidemic. As shown in this report, climate factors may have contributed to the recent large outbreak in northern Sweden.

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Dr Pettersson is a clinical virologist working at the Umeå University Hospital. Her major research interest is the biology and epidemiology of hantaviruses.

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Age group, y	No. (%) cases
<1–4	1 (0.20)
5–14	16 (3.3)
15–24	34 (7.0)
25–34	48 (9.8)
35–44	82 (17)
45–54	89 (18)
55–64	103 (21)
65–74	78 (16)
75–84	32 (6.6)
85–94	5 (1.0)
Total	488 (100)

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識別番号・報告回数		報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
一般的名称	-	研究報告の公表状況	http://www.boston.com/news/local/articles/2008/05/13/1_dies_ill_after_receiving_kidneys?mode=PF	公表国	使用上の注意記載状況・ その他参考事項等
販売名(企業名)	-			米国	
研究報告の概要 99	<p>ボストン病院で一人の臓器提供者から腎臓移植を受けた70歳の女性が死亡し、57歳の男性が重態となった。臓器提供者は回復不能な脳障害をこうむった49歳のホームレスの男性で、エイズウイルス、B型肝炎、C型肝炎などについては検査されていたが、2005年にマサチューセッツとロードアイランドで3人の移植患者が死亡した際と同じ病原体である「リンパ球性脈絡髄膜炎ウイルス(LCMV)」に感染していた。</p> <p>このLCMVは、一般的にげっ歯類によって伝播し、健康な人々ではインフルエンザ様の症状で特に問題はない。臓器移植の際には、臓器の組織損傷を防ぐため、エイズウイルス、肝炎、ヘルペスのような容易に検査できる病原体は検査されるが、あまり一般的ではなく、時間のかかるLCMVのような病原体は検査されない。</p> <p>移植を受けた女性は、家に帰ってすぐ具合が悪くなり(発熱、下痢などの、腎に特有でない症状)、外科手術のおよそ2週間後に再入院したが、さらに悪化し死亡した。</p> <p>もう一例の男性は外科手術の2.5週間後に発熱で再入院しており、集中治療室で抗ウイルス薬を投与されている。CDCにおいて、死亡した臓器提供者と移植を受けた患者2人の検体が検査したところ、LCMV陽性であることがわかり、臓器提供者からの伝播であることが確認された。</p>				
	報告企業の意見	今後の対応			
リンパ球性脈絡髄膜炎ウイルスは、エンベロープを有するアレナウイルス科のRNAウイルスで、直径60~280nmの多形性であるので、ウイルス除去膜処理、加熱処理などにより、物理的除去又は不活化されると考えられる。	今後とも、リンパ球性脈絡髄膜炎ウイルスに関する情報に留意していく。				

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