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Nephropathia epidemica: incidence of clinical cases and antibody prevalence in an endemic area of Sweden

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SUMMARY

The incidence of nephropathia epidemica (NE) was compared with the NE antibody prevalence in normal population in a highly endemic area of Sweden (Västerbotten county). The antibody prevalence rate in the oldest age groups were found to be 14 and 20 times higher than the accumulated life-risk of being hospitalized with NE for men and women respectively. Whether the infection in persons not admitted to hospital is subclinical, atypical or clinically fulminant, remains to be determined.

INTRODUCTION

Nephropathia epidemica (NE), a member of the haemorrhagic fever with renal syndrome complex, was first described by Zetterholm (1934) and Myhrman (1934). Until recently this human disease has been defined only by clinical symptoms: sudden onset of fever, abdominal or low back pain, renal involvement and spontaneous recovery (Lähdevirta, 1971; Nyström, 1977).

The aetiological agent of NE, Puumala virus, was isolated in 1983 from a bank vole (*Clethrionomys glareolus*) (Niklasson & LeDuc, 1984). This virus isolate made serological confirmation of clinical cases possible as well as providing a tool for sero-epidemiological surveys.

Niklasson & LeDuc recently conducted a nation-wide study of NE in Sweden, identifying its major endemic area (Niklasson & LeDuc, 1987). This study showed that NE incidence as well as antibody prevalence is highest in an area around the 64th parallel. In that region a high infection rate among bank-voles, the main reservoir of NE, was also observed.

Table 1. *Residents in Vindeln, Sorsele and Norsjö tested for specific anti-Puumala virus antibodies*

Age group	Number of residents		Clinical cases		Incidence*		Positives/sera tested (%)	
	M	F	M	F	M	F	M	F
0–9	1385	1342	0	0	0·000	0·000	0/0	0/0
10–19	1700	1599	5	0	0·210	0·000	1/6 (17)	0/7
20–29	1229	1021	18	3	1·046	0·210	1/16 (6)	1/47 (2)
30–39	1102	1080	13	2	0·843	0·132	3/20 (15)	2/29 (7)
40–49	1342	1252	11	3	0·586	0·171	2/15 (13)	1/31 (3)
50–59	1412	1257	2	4	0·101	0·227	3/25 (12)	10/41 (24)
> 60	1999	1945	2	1	0·072	0·037	44/111 (40)	14/91 (15)
Total	10169	9496	51	13	2·858	0·777	54/193 (28)	28/246 (11)

* Incidence is calculated as the number of clinical cases of NE per 1000 inhabitants/year.

The aim of the present study was to compare NE incidence recorded over 14 years with antibody prevalence rates in a highly endemic area.

MATERIALS AND METHODS

As part of an earlier study, hospital files from the departments of medicine, infectious diseases and pediatrics were investigated in Västerbotten county for NE cases (Nyström, 1977). Information on age, sex and area of residence were collected between December 1959 and April 1974 for all cases fulfilling the clinical criteria of NE. The criteria used for discriminating cases of NE were; sudden onset of symptoms, pyrexia, abdominal or low-back pain, gastrointestinal symptoms, proteinuria, raised serum createnine concentration, uneventful course and spontaneous recovery.

Three Swedish municipal districts in Västerbotten county (Vindeln, Sorsele and Norsjö) with high incidence rates were selected for this study. The population of these three areas was divided into sex and age groups and the number of residents was recorded as the mean for census years 1960, 1965, 1970, 1975. The accumulated risk of contracting NE during a life-time is calculated from age-specific incidence rates for each decade. The incidence rates per decade were then added together.

Serum specimens were collected in 1985 from patients visiting the out-patient clinic in Vindeln, Sorsele and Norsjö regardless of the reason for the visit and previous history of infectious diseases. The sera were sent frozen to the National Bacteriological laboratory and stored at −20 °C until tested.

All sera were tested by an immunofluorescent antibody (IFA) assay against Vero-E6 cells infected with Puumala virus (strain Vindeln) as described elsewhere (Niklasson & LeDuc, 1987).

RESULTS

The total number of inhabitants in Vindeln, Norsjö and Sorsele together with the number of clinical cases of NE are shown in Table 1. In the male population a clear incidence peak is seen in the age group 20–29 years of age, then slowly

declining. In the female population the incidence-rates are more constant over their adult life. No NE infection was recorded in children under the age of 9.

The results from sera collected in Vindeln ($n = 248$), Norsjö ($n = 90$) and Sorsele ($n = 101$) tested on Puumala virus-infected cells are also shown in Table 1. Antibody prevalence rates increased with age and reached approximately 40% in males and 15% in females in the age group of 60 years or older. The male:female ratio for the accumulated risk of contracting NE during a life time was 3·7:1. This is comparable with the sex-ratio of 2·6:1 for antibody prevalence in the age group 60 years and older.

DISCUSSION

Earlier work by Nyström (1977) and a recent study by Niklasson & LeDuc (1987) have established that Västerbotten county is a highly endemic region for NE. It is likely that the incidence figures in this study are an underestimate of the true number of clinical cases. During field trips into endemic areas, several typical as well as mild cases of NE were found that did not have medical attention at the time of infection but later serology made the NE diagnosis likely (B. Niklasson & L. Nyman, unpublished data).

The life-time incidence of hospitalization with NE in this area is 2·9% for men and 0·8% for women. To compare this frequency with the antibody prevalence rates in the older age groups we must assume that NE infection does not affect the mortality in the population and that NE infection induces lifelong persisting antibodies detectable by IFA. Furthermore we must assume that the endemic situation has been constant when comparing clinical attack rates recorded during the period 1959–74 with results of serology performed in 1985 when the sera were collected. The antibody prevalence rate in the oldest age group is 40% for men and 15% for women). These figures indicate that there are 14–20 NE infections per case of NE hospitalized for men and women respectively. If the assumption that NE infection does not affect population mortality and/or that NE antibodies persist for life are wrong, the ratio of infections per hospitalized case will increase.

In the survey by Niklasson & LeDuc, 243 serologically confirmed cases were recorded during a year when the vector, *Clethrionomys glareolus*, was prevalent in the endemic region of Sweden. Extrapolating from the ratio of infections per recorded cases this suggests more than 4000 cases during that year. These cases occurred in a population of 2300000 living in the endemic area of Sweden. Although the calculations made above are based on approximations and not intended to be exact it indicates the magnitude of NE infections.

It remains to be determined whether the clinical presentation in cases not getting medical attention are typical, atypical or mild or if some cases of NE are asymptomatic. However, it is clear that NE is a significant human pathogen in the endemic part of Sweden.

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REFERENCES

LÄHDEVIRTA, J. (1971). Nephropathia epidemica in Finland. A clinical, histological and epidemiological study. Thesis. *Annals of Clinical Research* **3**, Suppl. 8.

MYHRMAN, G. (1934). En njursjukdom med egenartad symptombild. *Nordisk Medicinsk Tidskrift* **7**, 793–794.

NIKLASSON, B. & LEDUC, J. (1984). Isolation of the nephropathia epidemica agent in Sweden. *Lancet* **i**, 1012–1013.

NIKLASSON, B. & LEDUC, J. (1986). Epidemiology of nephropathia epidemica in Sweden. *Journal of Infectious Diseases* **155**, 269–276

NYSTRÖM, K. (1977). Incidence and prevalence of endemic benign (epidemic) nephropathy in AC county, Sweden, in relation to population density and prevalence of small rodents. Thesis. *Acta Medica Scandinavica*, Suppl. 609.

ZETTERHOLM, S. G. (1934). Akuta nefriter simulerande akuta bukfall. *Svenska Läkartidningen* **31**, 425–429.