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ORIGINAL ARTICLE

New cases of suspected HFRS (Hantavirus infection) in south-eastern Poland

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Abstract

Introduction: HFRS – hemorrhagic fever with renal syndrome, found in Europe, is an acute viral zoonosis due to the hantavirus infection. The disease is characterized by the triad of symptoms: sudden, febrile onset, acute renal failure and haemorrhagic diathesis. The range of hantavirus infections in humans has not been yet established on the territory of Poland. The medical literature described 18 cases of seropositive HFRS in Poland – mainly in the district of Sanok, and single cases in the districts of: Brzozów, Dębica, Krosno, Lesko, Przemyśl and Stalowa Wola.

Aim: The aim of the study was to verify the hypothesis, assuming that patients hospitalized in the Department of Nephrology, located in the Regional Hospital in Przemyśl were infected with hantavirus and had HFRS.

Material and methods: Due to the fact that patients selected for the study were not tested serologically, verification was based on statistical comparison of the retrospectively selected group of patients suspected of HFRS with the seropositive group described in the study of Nowakowska, Heyman, Knap et al. in 2009, in terms of individual symptoms prevalence in conjunction with the structure of selected clinical and epidemiological parameters.

Results: 26 individuals with renal failure and influenza-like episode of several-day fever of unknown origin were indentified on the base of the retrospectively analyzed records of the patients hospitalized in the Department of Nephrology in Przemyśl between 2001–2011. The significant differences in age, frequency of selected laboratory parameters (platelet count, serum electrolytes) and oliguria were not found in both compared groups. However, the study group included the higher percentage of men. Additionally, the differences in prevalence of symptoms (cough, diarrhea), which are not considered specific for HFRS were detected. Analogously to the reference group, seasonal morbidity was observed also in the study group, but the peak intensity was delayed for 4 weeks.

Conclusions: The hypothesis cannot be rejected that, the group analyzed in the prestent study, hospitalized in the Department of Nephrology in the Regional Hospital in Przemyśl – is the sample of patients with HFRS (similarly to the group described by Nowakowska et al.). The cases described in this study can be considered as suspected of HFRS. It is justifiable to perform serological testing in these individuals.

Key words

Hantavirus Infections – diagnosis, Hantavirus Infections – epidemiology, South-Eastern Poland

INTRODUCTION

Hantaviruses, belonging to the *Bunyaviridae* family, have been present in Eurasia, both Americas and probably Africa. The hantavirus genus includes approximately 29 genotypes and 22 serotypes of virus. In Europe, *Dobrava* (DOBV) and *Puumala* (PUUV) [1] serotypes have been isolated most commonly; however, serotypes *Tula* (TUUV) and *Saaremaa* (SAAV) have also been isolated in recent years [1]. The infected rodents (mainly of the muridae genus) excreting the virus in faeces are considered to be the reservoir and vector in the environment. The infection is transmitted by inhalation of dust containing rodent faeces or by direct contact.

Two clinical syndromes caused by hantavirus infection have been described: HCPS – *hantavirus cardiopulmonary syndrome*, prevalent mainly in America, and HFRS-*haemorrhagic fever with renal syndrome*, found in Eurasia. The epidemic nephropathy, a benign disease caused by the *Puumala* serotype, prevalent mainly in Scandinavia, is considered to be a separate manifestation of HFRS. Pathogenesis of the renal failure in HFRS has so far not been completely understood. Nephrology textbooks [2, 3] classify hantavirus infection as an acute tubulo-interstitial nephritis. The spectrum of the HFRS clinical symptoms depends on the etiological factor serotype, a typical 5-phase course with rapid, febrile, 'flu-like' onset has been described in the literature [4]; most infections, however, are asymptomatic [5, 6].

In Slovakia, bordering with the Sub-Carpathian Region, reports of HFRS have been present for years [7]. The first report of hantavirus incidence on Polish territory dates from 1998, when a Korean-Polish-American group of researchers isolated viruses from *Microtus arvalis* [8] rodents captured near Łódź. However, serologically confirmed cases were not been reported in humans until 2005. The first outbreak of infections in Polish patients with clinical signs was detected and serologically confirmed in 2005 in Brzostek (1 case) [9] and in 2007 (17 cases from the districts of Sanok, Lesko, Brzozów, Krosno, Przemyśl and Stalowa Wola described in the article of Nowakowska, Heyman, Knap et al. [10]). Therefore, it is reasonable to claim that the Sub-Carpathian Region is an area of endemic prevalence of the hantavirus infection.

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In the autumn of 2007 and 2010 (October – December), in the Regional Hospital in Przemyśl, cases of the disease with an acute, febrile onset were observed, mostly in young men who were sent to the Department of Nephrology because of proteinuria and/or elevated creatinine values with suspected acute glomerulonephritis and renal failure. Polyuria, and normalization of the creatinine and urea values were observed in the course of hospitalization.

After retrospective analysis of the records made in March 2011, the patients were classified as suspected of HFRS, because the spectrum of clinical symptoms and course of dynamics in the above cases was similar to the data from literature.

OBJECTIVE

The aim of the study was to verify the hypothesis assuming the presence of HFRS patients infected with the hantavirus in the Department of Nephrology of the Regional Hospital in Przemyśl.

MATERIAL AND METHODS

Due to the fact that serological testing had not been performed in patients selected for the study, verification was based on statistical comparison of the isolated group of individuals suspected of HFRS with the seropositive group described in the study of Nowakowska, Heyman, Knap et al. in 2009 [10], in terms of the prevalence of individual symptoms and structure of selected clinical and epidemiological parameters.

Retrospective analysis included records of all patients hospitalized because of acute renal failure in the Department of Nephrology in the Regional Hospital in Przemyśl in 2000–2011. Criteria for inclusion in the study were:

1. acute, febrile onset of the disease;
2. morbidity in the autumn and winter (September to February);
3. undetermined etiology;
4. elevated creatinine (CREA> 1.2mg%), compared with normal laboratory values, or proteinuria occurring in first week of the disease (the phenomena had to be present at the time of admission to the Department of Nephrology, or in past medical history)[1].

The group of 23 individuals hospitalized in 2001 (1 pers.), 2007 (10 pers.) and 2010 (12 pers.) was enrolled. Subsequently, 3 patients hospitalized in January and February 2011 were incorporated into the group – assuming that they represented the outbreak of cases from 2010. The reason for the members of the study group seeking medical attention was a several-day fever (≥ 3 days) with sudden onset of flu-like symptoms, I,e. myalgia/arthralgia, abdominal pain, nausea, vomiting, diarrhea – in a variable configuration. 16 patients were admitted to the Department of Nephrology from the environment through the hospital emergency departments or clinics. 2 persons were transferred from Departments of Infectious Diseases, 1 from the Department of Surgery, and 1 from The Department of Gastroenterology (hospitalization in the above departments because of abdominal pain/loose stools), the next person, complaining of headaches, was hospitalized in the Department of Neurology with suspected subarachnoid haemorrhage prior to admission, and 5 persons were hospitalized in Departments of Internal Diseases. The period between onset of symptoms and admission to the Department of Nephrology was a maximum of 7 days.

The cases occurred in the 36th – 52nd week of the year (median, 47th week of the year). Inclusion of the persons admitted in 2011 for analysis (3rd, 6th and 7th week of the year was construed as consecutive weeks of the 2010 epidemic) which resulted in a median of the highest morbidity in the 48th week of 2010 (first half of December) for persons hospitalized in the 2010–2011 season.

The cases were observed in the former Przemyśl Region, i.e. in the districts of Przemyśl (15 pers., including the city of Przemyśl – 3 pers.), Jarosław (4 pers.), Przeworsk (6 pers.) and Lubaczów (1 pers.). 4 persons (15%) lived in urban areas (1 in Jarosław and 3 in Przemyśl), the remaining 22 were residents of rural areas.

The place of residence of members of the group and the order of disease onset in the epidemics of 2007 and 2010/2011 are shown in Figure 1. Geographical regions inhabited by the group members (according to the Kondracki decimal classification [11]) are summarized in Table 1.

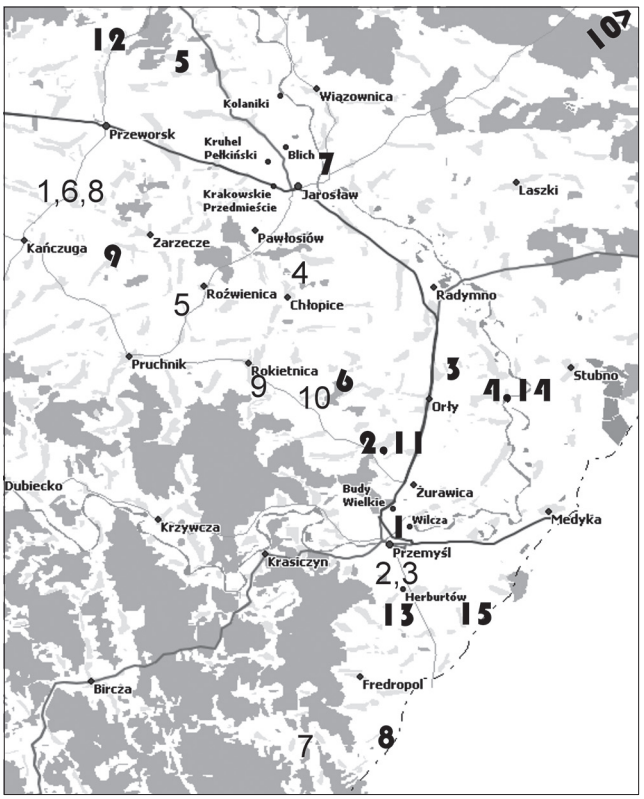

Figure 1. The area of prevalence of the suspected cases and their order.
The epidemic of 2007 – normal fonts
The epidemic of 2010/011 – thick fonts

The patients were of working age (mean age 36.5 ± 14.9 years), 1 person was older (79 years). The group was almost exclusively male (1 woman was hospitalized in January 2011). A broad-spectrum antibiotic was used in the treatment of all patients. In each of the cases, serum creatinine and urea levels

1. It should be mentioned that the study group included individuals with normal CREA levels during hospitalization in the Department of Nephrology – the abnormalities were observed prior to the admission.

Table 1. Geographical Regions [11] inhabited by members of the study group.

Sub-provinces	Mesoregions	No.	Percentage
Podkarpacie Północne	Dolina Dolnego Sanu 512.46*	7	26.9
	Płaskowyż Tarnogrodzki 512.49	1	3.8
	Pradolina Podkarpacka 512.51	2	7.7
	Podgórze Rzeszowskie 512.52	11	42.3
Zewnętrzne Karpaty Zachodnie	Pogórze Dynowskie 513.64	1	3.8
Podkarpacie Wschodnie	Opole Zachodnie 521.11	3	11.5
Beskidy Wschodnie	Góry Sanocko-Turczańskie 522.11	1	3.8

*Numbers acc. to the Federation Internationale de Documentation, Regionalisation of Europe. La Haye 1971

were normalized, recovery of the normal diuresis occurred, and the discharge from the department, on average, was on the 16th ± 7 days of the hospitalization (min. 7 days, max. 39 days).

The above-characterized group of 26 individuals (study group – A) was compared with the data of the group of 13 persons with confirmed HFRS, described by Nowakowska et al. [10] (control group – B). The null hypothesis assumed A=B. The groups were compared in terms of:

1. Epidemiological parameters
   1.1. Age and gender of the patient.
   2.2. Date of disease onset.
   3.3. Altitude of residence (above sea-level).
2. Parameters describing the clinical course of the disease:
   1.1. Frequency of the symptoms: (diarrhea, cough, haemorrhagic diathesis – cutaneous petechiae, ecchymoses).
   2.2. Frequency of abnormal laboratory findings (thrombocytopenia, elevated values of transaminases or creatinine, compared with laboratory norms, electrolyte disturbances – hyponatraemia, proteinuria, haematuria).[2]
   3.3. Percentage of individuals requiring haemodialysis.

Data were statistically analyzed using the Statistica 7 software (StatSoft).

RESULTS

The structure of the 2 groups was compared in the terms of age. The mean and variance values were different, but the differences were not statistically significant (p=0.7 for ANOVA test) (Tab. 2).

Gender ratio in both groups was also different, the control group consisted of 46.1% of women, whereas the study group – 3.9% (1 person). For the Chi-Square test, significance level was p=0.001.

2. PLT<150 K/µl; ASAT >34U/L; ALAT >44U/L; CREA > 1.2 mg/dl; Na < 136mmol/l; Erytrocytes > 4 wpw (in the visual field)

Table 2. Comparison of age between members of the study group and control group.

Group	Mean (y)	No.	Stand. dev.	Variance
Study (A)	36.5	26	14.9	221.5
Reference (B)	34.7	13	11.1	122.9
A + B	35.9	39	13.6	185.3

Date of the disease onset: the mean and median values in both groups were different. In both 2007 and 2010, the disease onset occurred later in the area included in the study, and the epidemic lasted longer than in the control group. Comparison of the 2 groups with ANOVA test resulted in a statistically significant result p=0.005. However, when considering only the 2007 cases, p=0.07 was obtained (Tab. 3). The study area covered the geographical Sub-Carpathian Region (Tab. 1) – only 2 cases of the disease were reported in individuals living in the Carpathian Mountains (Tab.1, regions 513.64, 522.11). In contrast, only 1 case was found outside the area of the Carpathians in the control group.

Table 3. Comparison of disease onset time in the study group and control group.

Year	Group	Week	No.	Stand. dev.	Variance	Min.	Max.	Range	Median
2007	Study (A)	46.1	10	3.8	14.8	40	51	11	47.0
	Reference (B)	42.8	13	4.4	19.0	32	48	16	43.0
2010/2011	Study (A)	48.7	16	5.6	31.0	38	7	21	48.5
	Reference (B)		0						
A+B		46.1	39	5.3	28.4	32	7	27	47.0

The altitude of residence was different in both groups – in the control group the average height was 472 ± 133 m (range of 157 – 600 m.a.s.l.), while in the study group, 225 ± 29 m (range 80–280 m.a.s.l.). Level of significance of rank differences in the Kruskal-Wallis test – p <0.001.

The spectrum of clinical symptoms in the compared groups was different: the study group had a lower frequency of physical signs, such as diarrhea or cough, and a higher frequency of proteinuria and elevated creatinine levels, compared to the control group. The frequencies of other disorders (including variations in laboratory tests) were comparable (Tab. 4). The percentage of persons requiring haemodialysis was similar in both groups.

Because of the fact that one of the criteria for inclusion in the study (i.e. the presence of renal failure at the time of admission or in the medical history) was related to the specificity of the Department of Nephrology, and was not present in the control group, randomization of both groups was attempted by comparing the prevalence of pathology (Tab. 4), considering only the individuals with elevated creatinine or proteinuria.

The Fisher test was used due to the limited sample size, results are shown in Tables 5 and 6. Significant differences in the number of incidencies of signs and non-significant differences in frequency of abnormal laboratory results were observed in both comparisons.

Table 4. Comparison of prevalence of disease symptoms /complication in the study group and control group.

Symptom	Percentage in study group	Percentage in reference group	No. below 5	chi-square 'p'	Fisher test, 'p'
Diarrhea	30.8	90.1	yes	0.0008	0.001
Cough	15.4	46.1	yes	0.04	0.05
Haemorrhagic diathesis (clinically overt)	15.4	100.0	yes	<0.0001	<0.0001
Thrombocytopenia	87.5	72.7	yes	0.28	0.27
Elevated transaminase (GOT, GPT)	68.0	90.9	yes	0.14	0.15
Elevated creatinine (CREA)	96.0	69.2	yes	0.02	0.04
Electrolyte disturbances	50.0	53.9	no	0.82	-
Proteinuria	100.0	76.9	yes	0.02	0.04
Haematuria	75.0	76.9	yes	0.9	0.61
Oliguria in the course of the disease	45.5	53.8	no	0.63	-
Haemodialysis in the course of the disease	26.9	38.5	no	0.46	-

Table 5. Comparison of prevalence of disease symptoms/complications in patients with elevated creatinine level.

Symptom	Percentage in study group	Percentage in reference group	Fisher test, 'p'
Diarrhea	33	86	0.02
Cough	13	56	0.02
Haemorrhagic diathesis (clinically overt)	17	100	0.001
Thrombocytopenia	87	57	0.12
Elevated transaminase (GOT, GPT)	71	86	0.4
Electrolyte disturbances	54	78	0.2
Proteinuria	100	89	0.29
Haematuria	73	89	0.32
Oliguriain the course of the disease	45	67	0.25
Haemodialysis in the course of the disease	29	56	0.16

Table 6. Comparison of prevalence of disease symptoms /complications in patients with proteinuria.

Symptom	Percentage in study group	Percentage in control group	Fisher test, 'p'
Diarrhea	30	88	0.007
Cough	17	50	0.07
Haemorrhagic diathesis (clinically overt)	17	100	0.0004
Thrombocytopenia	91	67	0.12
Elevated transaminase (GOT, GPT)	70	89	0.26
Electrolyte disturbances	57	70	0.37
Elevated creatinine (CREA)	96	80	0.21
Haematuria	74	100	0.09
Oliguria in the course of the disease	45	70	0.18
Haemodialysis in the course of the disease	30	50	0.25

DISCUSSION

Age structure of the study group was comparable with the control group, but a statistically significant difference was observed in the gender structure – the study group was almost exclusively male. The quantitative predominance of males among patients with HFRS has been confirmed in the literature [12], and a substantial majority of men has been observed in a study analyzing morbidity in Croatia [13] where HFRS epidemics occurred primarily during the war in the 1990s, and infections reported in young men on active military service. Reports from Finland [14] (retrospective analysis of 126 cases of epidemic nephropathy) have also confirmed the quantitative superiority of males (99 males to 27 females, the proportion of females being significantly higher than in the presented study, chi-square p=0.04). The predominance of males seems to be due to the greater exposure to infectious material (exposure to organic dust during field/farm related work, forestry, wood cutting and processing, etc.), but immunological factors affecting the distribution of the infections in the population have also been assumed to exist [13].

In epidemiological terms, the study group had a distribution of morbidity shifted by approximately 3–4 weeks, compared to the group from the study in Rzeszów. The regularity was observed in patients of the 2007 and 2010 epidemics. This situation cannot be explained by the technical imperfection of the study (i.e. comparing the date of admission to the Department of Nephrology in the study group with 'disease onset' in the control group), because the interval between onset and hospitalization in the Department of Nephrology ranged from 3–7 days in the study group (acc. to the records). The difference may be due to geographical conditions (residence in different geographic sub-provinces among the members of the compared groups) and climate (significantly lower altitude of residence of the study group in comparison to the control group). Furthermore, regional timeline differences in the distribution of the HFRS morbidity have been found within Europe – for example, in Croatia, where the peak intensity of the disease was observed in June and July [13]. To explain the differences between the compared groups, it can be hypothesized that the vegetative season in the area inhabited by the study group (Sub-Carpathia) was longer than in the Carpathian Mountains, which caused the delayed migration of rodents to the human habitats in autumn.

It should be noted that direct contact with rodents (vectors of infection) or their faeces, e.g. exposure to organic dust during work, is an important factor for suspected hantavirus infection. In the study group, data about contact with rodents or confirmed observation of rodents in the direct environment were not obtained from all patients. However, such contacts cannot be excluded (farm work, woodcutting, etc.) due to the fact that most of the members (85%) of the study group were residents of rural areas. In addition, hantavirus has been reported to circulate among domestic animals and livestock infected through the contact with rodents or their faeces [15]. Therefore, contact with rodents may not be a condition necessary for HFRS incidence, despite the absence of data on cases of human infection from domestic animals.

In the course of the presented study, significant differences in the number of signs between the compared groups were observed – a lower rate of reported disturbances, such as diarrhea, cough and signs of haemorrhagic diathesis

(erythema, petechiae) was demonstrated among the group in the Department of Nephrology in Przemyśl, compared to the control group. However, the study did not observe statistically significant differences in the number of laboratory parameters measured with absolute values (thrombocytopenia, electrolyte imbalance), or symptoms referred to as abnormal, according to the critical cut-off points (oliguria, etc.), which have been well-established in the literature and clinical practice.

The obtained differences in the number of quality parameters could be due to the research method used (retrospective analysis) and the lack of standardization of anamnesis techniques and documentation, not only between the compared groups, but also in the study group (different doctors examining the patients). Differences may be also caused by the clinical course of the disease, apart from in the control group, because HFRS symptomatology exhibits regional variation, conditioned by the dominant virus serotype in the relevant area. According to Knap [4], diarrhea has not been considered a typical symptom of hantavirus infection in Poland, and sometimes cough has not been mentioned in the clinical characteristics of HFRS [12]. Notably, guidance in the clinical symptoms of HFRS in Poland cannot be clearly determined, because only 18 confirmed cases have been described.

Książek et al. [2] classify hantavirus infection as an acute tubule-interstitial nephritis, characterized by damage mainly to interstitial tissue and renal tubules, as confirmed by the kidney biopsies of patients in acute phase of the disease [12]. Interstitial haemorrhage, oedema and inflammatory infiltrates composed of lymphocytes and monocytes were observed in these individuals. It should be noted that the pathogenesis of the renal damage in HFRS remains incompletely understood. Interstitial nephropathy is characterized by the presence of moderate proteinuria (about 1–2 g/day), whereas nephrotic proteinuria was observed in the study group in the initial stage of the disease. The patients were therefore sent to the Department of Nephrology with suspected acute glomerulonephritis. The hypothesis that the group analyzed in the study had HFRS cannot be rejected, despite non-compliance with the expectations of the clinical course, because 14 cases of serologically-confirmed HFRS with a clinical course similar to the present study have been reported in France, in the region of *Ille de France* [16]. In the above-mentioned group of 14 patients hospitalized in various departments (including the Department of Nephrology), rapidly progressive glomerulonephritis was initially suspected because of the acute renal failure with active urine sediment, severe proteinuria and acute, febrile onset. Therefore, immunological tests were performed in 10 individuals (complement levels, ANA, etc.), and renal biopsy in 2 patients. Differences in the picture of the disease in various countries and geographical regions are probably due to the different serotypes of viruses causing the HFRS.

CONCLUSIONS

1. The null hypothesis that the group of people analyzed in the presented study is the sample of patients with HFRS cannot be rejected because of similarity to the group described by Nowakowska et al., and permission to ignore the observable differences.
2. The shift of the peak morbidity in the study group in comparison to the control group may be explained by geographical and climatic differences.
3. It seems justified to determine the symptomatology of HFRS typical for Poland, based on comparison of the serologically-confirmed cases (including determination of the virus serotype).

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