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CHARACTERISTICS OF HEMORRHAGIC FEVER WITH RENAL SYNDROME IN FORMER YUGOSLAVIA IN WAR CONDITION*

KARAKTERISTIKE HEMORAGIČNE GROZNICE S BUBREŽNIM SINDROMOM U BIVŠOJ JUGOSLAVIJI U RATNIM USLOVIMA*

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Abstract

From the first case of hemorrhagic fever with renal syndrome (HFRS) in former Yugoslavia in 1952, and first epidemic 1961, sporadic cases and epidemic appeared frequently. So far different hantaviruses have been isolated, from lung of rodents and human speciments.
The largest epidemic of HFRS, in Europe was registered in former Yugoslavia in 1995 year, during the war, in Bosnia and Herzegovina. More than 3.000 cases, predominantly soldiers, were infected with different serotypes of hantaviruses. By indirect immunofluorescent test (IIFT) and ELISA IgM, as HFRS were confirmed 481 cases. By IIFT sera have been tested with Hantaan (HTN), Puumala (PUU), Seoul (SEO), and Belgrade (BGD) viruses. By (ELISA) IgM, sera tested with HTN and PUU antigen. Following immune response, patients grouped in four groups. Sera in groups 1 and 2, in which include 346 patients (72%), by IIFT primarily reacted with HTN, SEO and BGD viruses, while by ELISA IgM, sera reacted by HTN with and or with out reactivity by PUU. In these groups, 90% patients had one of the renal symptoms: macrohematurija, proteinuria, anuria, oliguria. 50% had hemorrhagic manifestation. 20% had respiratory symptoms. Incomplete data show that 7 patients from groups 1 and 2 died. To groups 3 and 4 belong 135 patients (28%), who reacted by IIFT primarily by PUU and with or with out reactivity by ELISA IgM with HTN. Disease among these group patients, tended to be clinically mild, resembling flu like illness. In some patients immune response differ from infection with Belgrade and PUU viruses.
Remarkably, HFRS cases appeared in two peaks: one in June, and another in August, while in patients with immune response to PUU-like infection, the peaks appeared in April and on June.
Circulation of more than two serotype hantaviruses, in former Yugoslavia, presents an extraordinary challenge for diagnosis, prevention and control. They all induce illnesses with a markedly different clinical courses and different prognosis.

Key words
hemorrhagic fever with renal syndrome, Belgrade, Hantaan, Puumala hanta-viruses.

Ključne reči
hemoragična groznica sa bubrežnim sindromom, Belgrade, Hantaan, Puumala hantavirusi.

INTRODUCTION

Hemorrhagic fever with renal syndrome (HFRS), acute virus nephropathy, is wildly distributed in the World. More then 14 serotypes viruses, from genus Hantavirus, family Bunyaviridae were registered. Many of them induce in humans two clinical form of illness: HFRS and hantavirus fever pulmonary syndrome (HPS).

HFRS in Europe and Asia induce: HTN, PUU, SEO, BGD, Dobrava (DOB), Tula (TUL), Tula/Čačak, Khabarovsk (KHB) hantaviruses (1-8). HPS in North and South America induce: Sin Nombre, New York, Black Creek, El Moro, Andes and another serovariant hantaviruses [9-13].

In Bosnia and Herzegovina, for the first time, hantavirus infection in humans has been recognized as emerging zoonoza in 1952 in a soldier, who was infected in the forest near Fojnica [14]. After that, clinically mild and severe form HFRS have been recorded annually through all former Yugoslavia [15-18]., with periodicall epidemics and mortality rates from less 1% to 16% [19].

The first epidemic of HFRS in former Yugoslavia occurred 60 km west from Belgrade, in military camp, in forest Fruška Gora. 46 soldiers were ill, from which 13 with severe form of disease and lethality 2.1% [20]. In next epidemic, in 1967, were more than 200 infected individuals with lethality 2.5%. Epidemic centered in forest area Fojnica-Bosnia and Herzegovina, Croatia (Plitvice Lakes) and in Montenegro [21,22,15]. Following epidemic in 1967, hantaviruses antigen were detected, in lung tissues in 8 out of 113 rodents Apodemus flavicollis and in 2 out of 17 Chlethrionomys glareolus captured in 1984 year.. Two isolated viruses from A. flavicollis and one from Cl. glareolus, were partially characterized. The isolates from A. flavicollis, designated Fojnica virus, were antigenic similar but not identical to Hantaan virus strain 76-118. The isolate from Cl. glareolus was antigenic indistinguishable from PUU virus [23]. From May until November 1986, an epidemic of HFRS occurred in all six Republics and two provinces of former Yugoslavia, with highest incidence in Montenegro and Serbia. Many patients, with serious clinical course, including severe renal insufficiency trombocitopenia and shock were hospitalized from which 11 patients died. Lethality in Montenegro was 9.09%, in Serbia 8%, while total lethality for former Yugoslavia was 6.8%. (no lethal cases in Slovenia, Croatia and province Vojvodina). It was the first epidemic, in one Balkan country, when clinical diagnoses HFRS were serologically confirmed, by IIFT, in 161 out of 276 suspected hospitalized patients [24]. During this epidemic, we also for the first time serologically confirmed 4 HFRS patients from Republic of Albania [24].

Already, from this epidemic, including analyze clinical course (which varied from mild to very severe form illness), immune response, and the fact that we confirmed that 11 species small mammals were and are infected with hantaviruses in nature, it was clear that in former Yugoslavia circulated more than 2 serotypes of hantaviruses [24]. In nationwide epidemic, in 1989, from 609 suspected cases as HFRS, were confirmed 226 HFRS cases. In Bosnia and Herzegovina and Serbia resided 182 cases. Severity disease differed, from region to region. Overall, lethality for former Yugoslavia was 6.6% [19]. Using two different methods and different hantavirus antigens, mortality rate in group patients with immune response to PUU was 0.9% but in the group which reacted primarily with HTN was 10.4%. Also, like in previous epidemic, no lethal cases in patients from Slovenia, Croatia and province Vojvodina. When differentiated infected people, with immune response by PUU, from infected with immune response by HTN, ratio between PUU and Hantaan was: Slovenia 8:2, Croatia 24:2, Bosnia and Herzegovina 55:58, Serbia was 4:43, Macedonia 0:6, Kosovo and Metohija 0: 29 and Vojvodina 0:2. All lethal cases in Serbia, Bosnia and Herzegovina and Kosovo and Metohija, belonged to group with immune response to HTN, except one in Bosnia and Herzegovina, who belonged to group with immune response to PUU. Mortality rate in Serbia, from infected people by to HTN related viruses, (HTN, SEO) was 18%, in Kosovo was 6.9% and in Bosnia and Herzegovina 11.3%. Following immune response, by two methods (IIFT and ELISA IgM) and 3 antigens (HTN, PUU and SEO), it was clear that beside HTN, and PUU viruses, in natural foci of HFRS, in former Yugoslavia, circulated and induce illness some new hantaviruses [19]. The same 1989 year, in the nine places: Slovenia, Croatia, Bosnia and Herzegovina and Serbia, with numerous HFRS patients, epizootiology investigation was done. Only, in two investigated foci in Serbia (Čačak and Požarevac), beside hantavirus infected A. favicollis, A. sylvaticus, Cl. glareolus and another species of small mammals was present, abundant and hantavirus infected species Apodemus agrarius [19, 24].

In 1992 we reported the isolation of new hantavirus, serologically related to HTN, rather than to PUU. Virus has been isolated, from blood and urine, of very severe HFRS patients. Patients were from central part of Serbia, where severe cases and infected rodents A. agrarius and A. sylvaticus appeared each year. It was excellent opportunity, to describe in details, clinical course after infection with this new virus named BELGRADE virus [4]. From other patient we isolated virus closely related to HTN virus named Kraljevo [4]. Later, we published data, about isolation Dobrava virus, from rodent lung Apodemus flavicollis captured in Republic Slovenia [5]. Presence of virus antigen, in lung of A.flavicollis from which DOBRAVA virus was isolated, also was done in national reference laboratory for hemorrhagic fevers in Belgrade.

In clinical course of HFRS patients from whom Belgrade virus has been isolated, beside renal insufficiency were present shock and pulmonary edema, as the main course of death in 9 out of 15 lethal cases in 1989 epidemic. Intubation and mechanical ventilation used without success [4].

Atypical serum neutralizing antibody response, to prototype strain of PUU viruses, in some patients, with HFRS, have been long suggested the existence of other hantaviruses in Balkan. Using reverse transcript-polymerase chain reaction, Tula virus RNA was amplified from hantavirus positive lung tissues of a European pine vole (Pitymys subterraneus). The P. subterraneus was captured in 1987, after outbreak of HFRS of soldiers, exercised in the field of Čačak region, in central part of Serbia [7].

The largest epidemic of HFRS in Europe was registered in former Yugoslavia in 1995 during war in Bosnia and Herzegovina.

MATERIAL AND METHODS

From May till September 1995, an epidemic of HFRS, with more than 3.000 cases occurred, in former Yugoslavia, with the highest incidence of soldiers, during the war in Bosnia and Herzegovina. For the better understanding, epidemic process we also show the number of 38 serology confirmed HFRS cases 6 mounts before, and 41 confirmed cases 6 mounts after epidemic year in the same localities.

Human sera: A thousand and three hundred sera, from 878 hospitalized patients are: from Bosnia and Herzegovina, Serbia (including Province Kosovo and Metohija), Montenegro and Macedonia. All were suspected of having HFRS, and referred to us, at the National Reference Laboratory for Viral Hemorrhagic fevers in Belgrade to be tested.

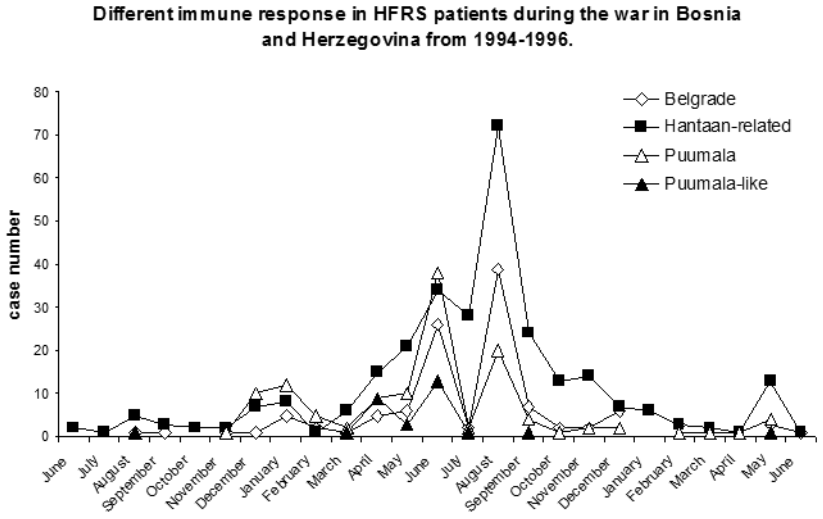
Methods of work: By the IIFT, sera tested for antibodies against HTN virus strain 76-118 [1]. PUU virus strain Hallnas1 [2], SEO [3] and Belgrade virus [4], using fluorescein isothiocyate-labeled goats antibodies to human immunoglobulin. Sera were tested from 1:32 up to 4.096 dilution using spot slides of Vero E-6 cells infected with hantaviruses as described previously (19, 24). Patients with typical symptoms of HFRS, but without serology confirmation and patients with titer of antibodies lower than 1:64 have been excluded from this study. Mostly samples of sera were taken between 4th and 14th days after onset of illness. By the ELISA IgM sera were tested on HTN and PUU antigen in dilution 1:100 up to 12.800 [19].

Table 1. Distribution of 481 HFRS cases per year in correlation with immune response to different hantaviruses during the war in Bosnia and Herzegovina in 1995.

	No *suspected*	TOTAL *serologicaly confirmed cases*	*Belgrade*	*Hantaan-related*	*Puumala*	*Puumala-like*
1994						
June	**22**	**2**		2		
July	**10**	**1**		1		
August	**18**	**6**	1	5		1
September	**11**	**5**	1	3		
October	**15**	**2**		2(1exitus)		
November	**12**	**4**	1	2(1exitus)	1	
December	**33**	**18**	1	7(1exitus)	10	
1995						
January	**53**	**25**	5(1 exitus)	8	12	
February	**15**	**8**	2	1	5	
March	**20**	**10**	1	6	2	1
April	**55**	**38**	5	15(1exitus)	9	9
May	**83**	**40**	6	21	10	3
June	**203**	**111**	26	34	38	13
July	**134**	**33**	2	28	2	1
August	**394**	**131**	39	72(3exitus)	20	
September	**139**	**36**	7	24	4	1
October	**59**	**16**	2	13	1	
November	**74**	**18**	2(1exitus)	14(1exitus)	2	
December	**71**	**15**	6	7	2	
1996						
January	**30**	**6**		6(1exitus)		
February	**23**	**7**	3	3	1	
March	**13**	**3**		2	1	
April	**11**	**2**		1	1	
May	**50**	**21**	3	13	4	1
June	**31**	**2**	1	1		

RESULTS

Of 1.300 sera from 878 patients with signs and symptoms suggestive of HFRS: sudden onset, of high fever, abdominal or back pain, retro-orbital headache, vomiting hemorrhagic manifestation (such as scleral hemorrhages, epistaxis, hemoptisis, ecchymoses), prolonged clotting time, proteinuria and or oliguria, 481 were found to have serological evidence of hantavirus infection. Mostly of them (320



out of 481) were infected during civilian war 1995 in Bosnia and Herzegovina, 30 are from Serbia, 34 from Kosovo and Metohija, 96 from Montenegro and 1 from Macedonia. Generally speaking, all they had similar condition for infection: temporary profession (soldiers), similar epidemiologic circumstances and type of exposition in the same biotope-forest. For the better understanding, epidemic process, we show results about number of 38 confirmed HFRS cases 6 months before and 41 cases six months after epidemic year in the same locations.

Of the 481 HFRS patients, 346 (72%) primarily reacted by HTN or to HTN related viruses (HTN, SEO, BGD). They belong to group 1 and 2, while 135 (28%) reacted principally by PUU. They belong to group 3 and 4.

In the first group were 103 (21.5%) patients. All they, by IIFT, reacted with proximately the same titers with HTN, SEO, BGD and PUU viruses. High titer IgM antibodies to HTN was present by ELISA test and with out reactivity by PUU. It is the same immune response, which was confirmed in patients from whom Belgrade virus was isolated. Clinical disease in this group tended to be severe. The incomplete data show, that two patients from about group died.

In the second group were 243 (50.5%) HFRS patients, which by IIFT, like patients in Korea and the people Republic of China, possessed high antibody titer by HTN and SEO and in our investigation also with BGD, with the much lower reactivity by PUU antigen. In ELISA IgM, antibody were present with both antigen, but with 4 or more highest titer by HTN then by PUU. Like, with patients from first group, clinical disease tended to be severe. Incomplete data show that 5 patients from this group died.

In first and second groups, 90% of patients had one of the renal symptoms: macrohematuria, proteinuria, oliguria, anuria; 50% had hemorrhagic manifestation, from which 75% belonged to patients locate in two mountains Ozren and Treskavica near Sarajevo; 20% had respiratory symptoms (bronchopneumonia).

In the third group were 107 (22.2%) patients who by IIFT and ELISA IgM like Scandinavian HFRS patients had high antibody titers to PUU antigen, and lower titer to HTN, SEO and BGD antigens. Clinical disease, among patients, tended to be moderate and mild in comparative with the group 1 and 2. No lethal cases in this group.

In the fourth group were of 28 (5.8%) patients. According immune response, location, and clinical disease, patients from this group appeared to be infected with a hantavirus which is distinct from PUU. Sera of patients, from this group, had striking high reactivity with PUU antigen by IIFT and by ELISA IgM, with absence IgM reactivity with HTN antigen. Diseases in this group, tended to be clinically mild, resembling a flu-like illness. In the clinical course, in hospitalized soldiers, were severe throat (they cannot swallow food and water). Temperature usually was not higher then 38oC. On day 4-5th, mostly patients developed rash, on neck and chest, and absent from the face. Remarkably, was hyperemia the gorge. Patients from this group were from north-west Bosnia and Herzegovina. They not had back and abdominal pains, so characteristic for HFRS in endemic regions. Oliguria, poliuria, urea and creatinin were all the time of illness normal. Only pathologic finding was slightly elevated transaminazes. No lethal cases in this group. Earlier, we confirmed HFRS patients with the same immune response and clinical course in camp of soldiers in the Central Serbia (Čačak region). Oliguria, poliuria, urea and creatinin was all the time of illness normal (unpublished data).

The most cases, during war, which were infected with HTN related viruses (HTN, BGD, SEO), appeared in two peaks, one in June and another in August. The patients with immune response by PUU, appeared in April, May and June with second peak in August, while in patients with immune response to Puumala-like virus peaks were in April and June.

DISCUSSION

HFRS was a major military problem in the world. In Bosnia and Herzegovina, during the war, the largest outbreak of HFRS in Europe occurred 1995 among the soldiers and civilians, located in the forests and fields for the long time. More than 3.000 people were infected. We now reported the illness among 481 serology confirmed HFRS cases, and different hantaviruses involving in epidemic process. Additional, published data also inform us that HFRS in the same year was registered inside of near 300 UN soldiers located in Tuzla region in Bosnia and Herzegovina (128 HFRS patients were serologically confirmed), [25]. The same year, in several localities in Croatia, from numerous suspected cases, HFRS was confirmed in 50 soldiers from whom two died [26]. In Slovenia in 1995, 14 HFRS cases (one fatal) were registered [27].

In Bosnia and Herzegovina, and another 5 Republics of former Yugoslavia, HFRS can be cause by HTN, SEO, BGD, DOB and PUU. Each of them, can results in markedly different disease, with quite different prognosis. It added a further level of complexity. When analyze number of patients with immune response in groups 1 and 2 (Table1 and Graph 1), it is clear that there are two peaks: one was in June, other, higher in August. In July number of patients infected with BGD virus decreased 13 times. From the sec-

ond group number of patients decreased in July less then 2 times. In group infected with PUU virus, higher firs peak was also in June and decreased in July 19 times. Second peak for PUU, in August, was 2 times lower then in June. In the fourth group patients, with new kind of PUU-like immune response, peaks were in April and June.

When tested 67 convalescent sera, collected 14 years after epidemic 1967 from area Fojnica in Bosnia and Herzegovina using the same methods and antigens, also 4 kind of immune response were found. (unpublished data).

These results are different from all another countries in Europe and European part of Russia, where most cases were infected with Dobrava, Sarema and Puumala viruses, registered in the autumn-winter and winter-spring time [28-30]. Difference appeared also in % of lethality. In the Croatia and Slovenia, before war no lethal cases [19, 31]. The first 2 lethal cases in Croatia were confirmed in 1992 inside of soldiers during the war. One was infected with Dobrava virus and another belonged to not identified hantavirus [32, 31]. The lethal cases in soldiers in Slovenia 1995, possible were results of infection on territory of Bosnia and Herzegovina during war [27].

The demonstration of these viruses which closely resemble to HNT and PUU were consistent with the serological data reported previously, and clinical observation of existence both severe and mild form of HFRS in former Yugoslavia [4, 5, 18-22, 24]. The disease severity differed from region to region. Following immune response in patients from Bosnia and Herzegovina in period from 1995 up to 2002 inside of 311 cases, 155 belonged group patients infected with Puumala, 72 were infected with Dobrava and 84 belonged to not identified hantaviruses [33]. Similar results were in Croatia too [34]. In publication from 2006 years, genetic investigation with limited human samples from epidemic 2002, confirmed that Dobrava/Belgrade strains responsible for the most of severe HFRS cases in Serbia and Montenegro [35].

Epizootiology investigation, during epidemic 1989, included 9 foci (Bosnia and Herzegovina, Croatia, Slovenia and Serbia where numerous HFRS cases were registered. 544 small mammals, predominantly rodents were examined to presence hantavirus antigen and antibody. Examination confirmed that, species A. agrarius was present, abundant and hantavirus positive only in foci in Serbia from which localities Belgrade viruses was isolated (Čačak and Požarevac). Also in Serbia the most abundant and frequently infected were some insectivore and A. sylvaticus with very rare Clethrionomys glareolus, which is the main host hantaviruses in Slovenia and Croatia [19, 24, 36, 37]. However, HFRS patients from eastern Bosnia, central part of Serbia, Kosovo, Macedonia and Montenegro, mostly had immune response to HTN serogroup (HNT, BGD,SEO) which are dominant virus strains in south and central part of Serbia, causing very serious form of disease, including pulmonary syndrome, as the most frequent cause of death [4]. Near the same number of clinical severe and mild HFRS cases were registered in Bosnia and Herzegovina in earlier described epidemics [19, 24]. During the epidemic, in 1995, in Bosnia and Herzegovina, most hospitalized patients had severe illness. 72% belonged to groups with immune response of infection by viruses related to HTN. In western Bosnia, Croatia and Slovenia PUU virus is dominant pathogen for humans, with very rare endemic foci of HTN related viruses [19, 25, 26, 38]. Described lethal HFRS cases in soldiers in Croatia and Slovenia 1995 possible were infected on territory of Bosnia and Herzegovina during war [26, 27].

Probably, a reason for higher percentage serology confirmed severe cases, during war, in Bosnia and Herzegovina, compared with previously described epidemics have been, that hospitals were occupied with very serious HFRS infected and wounded people.

Apstrakt

Od prvog slučaja hemoragične groznice sa bubrežnim sindromom (HGBS) u bivšoj Jugoslaviji 1952. godine, i prve epidemije 1961., sporadični slučajevi i epidemije beleže se učestalo. Do sada su, u bivšoj Jugoslaviji, izolovani različiti serotipovi hantavirusa, iz pluća glodara i humanog materijala.

Najveća epidemija HGBS, u Evropi, registrovana je 1995.godine, za vreme rata u Bosni i Hercegovini. Više od 3.000 slučajeva, pretežno vojnika inficirano je različitim serotipovima hantavirusa. Serološkim metodoma indirektne imunofluorescencije (IIFT) i ELISA IgM testom, infekcija hantavirsima dokazana je kod 481 hospitalizovanih slučajeva. Testom IIF serumi su testirani na Hantaan (HTN), Puumala (PUU), Seoul (SEO) and Belgrade (BGD) hantaviruses. ELISA IgM testom serumi su testirani sa HNT i PUU antigenom. Na osnovu imunog odgovora oboleli su klasifiovani u 4 grupe. Serumi grupe 1 i 2, a u kojoj se nalazilo 346 bolesnika (72%), testom IIF snažno je reagovalo sa HNT, SEO, i BGD, dok u testu ELISA IgM serumi su snažno reagovali sa HTN sa ili bez reakcije sa PUU antigenom. U tim grupama, 90% obolelih imaju jedan od renalnih simptoma: makrohematuriju, proteinuriju, anuriu, oliguriu. 50% je imalo hemoragične manifestacije, 20% je bilo sa respiratornim simptomima. Prema nepotpuni podatcima 7 obolelih iz grupe 1 i 2 završilo je letalno. U grupama 3 i 4, a prema imunom odgovoru, bilo je 135 bolesnika (28%). U tim grupama IIF testom i ELISA IgM testom, serumi su reagovali sa PUU antigenom sa ili bez reaktivnosti sa HNT antigenom. Klinička slika kod obolelih ovih grupa bila je blaga, slična gripu, bez letalnih ishoda. U jednog broja obolelih imuni odgovor se razlikovao od obolelih inficiranih HNT, BGD i PUU hantavirusima.

Upečatlčjiva je bila pojava HGBS u dva talasa. Najbrojnija pojava slučajeva inficiranih HNT, BGD i SEO bila je u Junu sa drugim vrhom u Avgustu, dok je kod inficiranih sa PUU ili PUU-srodnim virusim vrh talasa bio u Aprilu i Junu.

Cirkulisanje više od dva serotipa hantavirusa, u bivšoj Jugoslaviji, predstavlja veliki problem u postavljanju dijagnoze, prevencije i kontrole bolesti. Svi ovi virusi izazivaju bolest sa uočljivim razlikama u kliničkoj slici i prognozi.

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