

HANTAVIRUS- SPECIFIC IgG AND IgM IN BALKAN ENDEMIC NEPHROPATHY (BEN) AND CHRONIC RENAL DISEASE

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Summary. Forty eight serum samples from patients with BEN and 41 from patients with other chronic nephropathies were assayed for antibodies to the Hanta virus (Hantaan and Puumala viruses) by Enzyme Immunoassay (ELISA). Hanta virus (Hantaan and Puumala) IgG and IgM antibodies were present in 18.8% of BEN patients, 8.3% cases positive and 10.4% cases with borderline values.

A total of 4/41 cases (9,8%) of non BEN chronic nephropathies (chronic pyelonephritis) had borderline values of antibodies for the Hantavirus.

No cases of 89 patients investigated by us had any sign of hantaviral infection: hanta virus pulmonary syndrome or haemorrhagic fever renal syndrome.

The relationship with the etiology of BEN needs further investigation.

Key words: Balkan endemic nephropathy, Hanta virus, antibodies

The etiology of BEN is unknown. Heavy metals, ionizing radiation, phenols, mycotoxins, viruses are incriminated.

Viral etiology is sustained by some observations: presence of virus-like particles in the renal tubular epithelium of BEN patients (1,2), isolation of coronaviruses from kidney biopsies of BEN patients (3), presence of antibodies to some viruses in BEN patients (3,4).

Recently, Hantavirus-specific IgG, IgM and IgA have been observed in acute and chronic renal disease in the United States (5).

Renal sequelae of Hantavirus infection and evolution to chronic disease are being discussed.

We have investigated Hantavirus specific IgG and IgM antibodies in BEN patients and in patients with other chronic renal disease from endemic and nonendemic areas.

Method

A total of 89 patients were investigated for the presence of IgG and IgM antibodies to Hanta (Hantaan and Puumala) viruses. Of these, 48 patients (35 of whom were hemodialysed) had BEN and 41 had chronic nephropathies: 5 had chronic glomerulonephritis (2 of whom were under CAPD), 31 had chronic pyelonephritis (5 of whom were hemodialysed, and one on CAPD), 2 had tubulointerstitial nephropathies (none of them were hemodialysed), 2 were polycystic kidney cases (2 of whom were hemodialysed), 1 had nephroangiosclerosis without dialysis.

The cases not undergoing hemodialysis or peritoneal dialysis showed chronic renal insufficiency.

Three patients with chronic nephropathies, other than BEN came from places where BEN had been detected.

We used: Hantavirus (Hantaan) IgG /Ig M ELISA (Enzyme Immunoassay) for the determination of IgG and IgM antibodies to the Hantaan serotypes and Hantavirus (Puumala) IgG/ IgM ELISA Enzyme Immunoassay for the determination of IgG and IgM antibodies to the Puumala serotypes produced by Progen Immuno-Diagnostika, Progen Biotechnik GmbH Heidelberg.

For calculation of the results, the ratio of the optical density (absorbance [A] of the patient sample and the reference control was determined).

$$\frac{A_{\text{serum}}}{A_{\text{reference-control}}} = Q$$

The Progen Immuno-Diagnostika interpretation of results for the IgG antibodies: Q<1 negative: no IgG antibodies specific for the Hantaan virus detected.

Q>1.5 positive: specific IgG antibodies to the Hantaan virus detected.

1<Q<1.5: no clear interpretation possible. The course of the disease should be monitored during 10 days. In case of suspected hantavirus, it is recommended to test the sample for Hantaan IgM antibodies and/or antibodies of the Puumala serotype.

For IgM antibodies: Q<1: negative: no IgM antibodies specific for the Hantaan virus detected.

Q>2: positive specific IgM antibodies to the Hantaan virus detected.

1<Q<2: no clear interpretation possible. The course of the disease should be monitored during 10 days.

In case of suspected hantavirus infection, it is recommended to test the sample also for Puumala IgM by ELISA.

For Puumala IgG/IgM antibodies there was the same interpretation. In case of suspected puumala virus infection it is recommended to test the sample also in Hanta-virus (Hantaan) ELISA.

In the cases in which Hantavirus (Hantaan and Puumala) values for IgG antibodies were: 1<Q<1.5 and for IgM antibodies 1<Q<2 they values were interpreted as borderline.

Results

Hantavirus antibodies were observed in 9/48 (18.8%) BEN patients (Table 1) and in 4/41 (9.8%) patients with nonBEN chronic nephropathies (Table 2). All nonBEN cases had chronic pyelonephritis and two of them lived in endemic villages.

Table 1. The occurrence of hantaviral antibodies in BEN patients (Q values)

BEN cases	Hantaan IgG antibodies	Hantaan IgM antibodies	Puumala IgG antibodies	Puumala IgM antibodies
1	2.157			
2	1.197 [#]		1.467 [#]	
3		5.969	1.031 [#]	1.470 [#]
4			1.761	1.291 [#]
5				1.194 [#]
6				1.351 [#]
7				1.244 [#]
8				1.047 [#]
9		1.201 [#]		
Total cases 9/48	2/48	2/48	3/48	6/48

([#] Borderline values)

Table 2. The occurrence of hantaviral antibodies in nonBEN chronic nephropathies (Q values)

Chronic pyelonephritis cases	Hantaan IgG antibodies	Hantaan IgM antibodies	Puumala IgG antibodies	Puumala IgM antibodies
1			1.027 [#]	
2			1.333 [#]	
3				1.161 [#]
4		1.201 [#]		
Total cases 4/41		1/41	2/41	1/41

([#] Borderline values)

The presence of Hantavirus antibodies in patients with BEN is difficult to discuss because none of the 89 patients investigated by us had any signs of disease caused by them: haemorrhagic fever, renal syndrome and hantavirus pulmonary syndrome.

In the United States, Patnaik et al. have shown Hanta virus positive serology IgG, IgA, IgM, in patients with acute and chronic parenchymal renal diseases: acute tubulointerstitial nephritis, necrotising glomerulonephritis,

IgA nephropathy, lupus nephritis, diabetic nephropathy and other disease, 68% of positive serum samples were positive for Hantavirus-specific antibodies: acute tubulointerstitial nephritis, necrotising glomerulonephritis and IgA nephropathy (5).

Rubini et al. found renal dysfunction or hypertensive vascular disease in 20% of patients who had hemorrhagic fever with renal syndrome (6). Le Duc et al. have reported an association of chronic renal disease, hypertension and Hantaviruses in the United States. They consider this virus as a possible cause (7). Settergren et al. consider that most of the patients recovered spontaneously without any evidence of chronic renal impairment (8).

Patnaik et al. have reported that approximately 10% of the idiopathic end stage renal diseases in Florida and California had a prior Hantaviral infection.

There is insufficient evidence that infection with Hantaviruses could predispose to chronic renal damage and end stage renal disease, but the issue needs further research.

In our patients with BEN and chronic renal insufficiency Hanta virus (Hantaan and Puumala) IgG and IgM antibodies were present in 18.8% of cases (8.3% positive and 10.4% at borderline values). 9.8% cases of nonBEN chronic nephropathies (chronic pyelonephritis), half of which living in endemic areas, antibodies for the Hantavirus were in a borderline range. Not a single case had any sign of Hanta virus infection.

We did not observe any relationship between Hanta-virus infection and BEN.

Our observation reveals the presence of Hanta serum antibodies in some patients with BEN on dialysis, but also in BEN patients at predialytic stage.

The possibility of chronic evolution of these patients after an acute infection with this virus and the implication of the etiology of BEN needs to be demonstrated.

Urinary tract tumors were frequently observed in patients with BEN (9,10,11,12). Uzelac-Keserovic et al. isolated coronavirus from kidneys taken from patients operated for urinary tract tumors (3).

In our study only one out of 48 causes had urinary tract tumor. He was positive for the Puumala virus.

Viruses are incriminated in BEN etiologies.

Apostolov and Spasic have suggested that BEN is a slow viral disease caused by coronavirus (2,13).

In Romania observation of titres of antiviral antibodies to some Papova viruses in BEN patients and in apparently healthy persons in endemic areas were reported by Stoian et al. (4).

The question of whether the viral infection remains in a latent state inducing a chronic affection of the kidney has also been raised. The existence of some viruses in a latent state, which might become active later is possible.

The haemorrhagic fever with renal syndrome (epidemic nephropathy) caused by the hantavirus was reported in South-East Asia and the Scandinavian countries (8,14).

Our findings of Hantavirus antibodies in some BEN

patients who had no history of haemorrhagic fever with renal syndrome imply that further studies are needed.

The presence of antibodies to Hantaviruses revealed by researchers in the United States in patients with

chronic renal diseases and by us in patients without BEN and outside the BEN area makes it very difficult to account for Hantaviruses in the etiology and pathology of this disease.

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