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Hypopituitarism as a Late Complication of Hemorrhagic Fever

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We report three patients who developed hypopituitarism as a late complication of hemorrhagic fever with renal syndrome (HFRS). Their past history, physical examination, and endocrine investigation confirmed hypopituitarism. Magnetic resonance imaging of the pituitary revealed atrophic pituitary gland with an empty sella. Hemorrhagic fever is endemic in certain regions of the Balkans, and this preliminary report suggests the importance of investigating the endocrine status in every patient who survived HFRS.

Key Words: Hypopituitarism; hemorrhagic fever with renal syndrome; pituitary apoplexy.

Introduction

Since it was first recognized in the 1950s during the Korean War with 3000 reported cases *(1)*, hemorrhagic fever with renal syndrome (HFRS) has often been diagnosed among soldiers of different armies and field workers in various countries. HFRS is an acute viral disease caused by RNA viruses that belong to the genus *Hantavirus*, family *Bunyaviridae (2)*. Two acute febrile diseases could result from infection with *Hantavirus*: Korean hemorrhagic fever, caused by Hantaan virus, and epidemic nephropathy, caused by Puumala virus. Both infections are prevalent in Asia (Korea) and Europe (Scandinavia and the Balkan peninsula). The hantaviruses are transmitted by rodents and represent a special danger to humans who have close contact with field rodents (field workers and soldiers). During the Second World War, a large epidemic of nephropathy with approx 10,000 cases occurred in German troups in Finnish Lapland *(3)*. In the former Yugoslavia, epidemic HFRS outbreaks have been recorded since the early 1950s *(4–6)*. A nationwide epidemic of HFRS occurred in 1989 with 226 cases with mortality rate of 6.6% *(7)*. In the military population, during the period 1952–1990, 84 patients with HFRS have been recorded *(8)*. During the recent military conflict in Bosnia, more than 300 patients with HFRS have been diagnosed, most of them soldiers, among them two from the multinational United Nations forces *(9)*. In the period from March to May 1999, six soldiers stationed in Kosovo were treated for HFRS *(10)*. Thus, these data confirm that military personnel are at high risk for the disease.

The clinical course of HFRS is characterized by fever, circulatory collapse with hypotension, hemorrhages, and renal failure. The disease progresses through the characteristic five phases: febrile, hypotensive, oliguric, diuretic, and convalescent. Most HFRS patients recover completely and complications are rare. Korean hemorrhagic fever has high mortality (5–10%) with striking hemorrhagic manifestations and shock, while the mortality from epidemic nephropathy is less than 1%. The analysis of 88 lethal outcomes of HFRS showed the occurrence of pituitary hemorrhage and necrotic foci in 75.5% of cases *(11)*. In patients who recovered, pituitary atrophy, secondary empty sella and clinically overt hypopituitarism have been reported only sporadically *(12–14)*. These findings suggest that patients with HFRS may have pituitary hemorrhage and subsequent necrosis with permanent pituitary failure. Here we describe three recent patients with unrecognized pituitary failure that developed as a chronic complication of HFRS.

Case Reports

Case 1

A 30-yr-old man was referred to our Institute for endocrine evaluation of hyperlipidemia resistant to statin treatment (Table 1). One and a half years earlier, he was treated for hemorrhagic fever with acute renal failure. HFRS was confirmed with positive serologic test for antibody to hantaviruses (indirect immunofluorescent antibody test positive in high titers, 1:1280). During the hospital course hemodialysis was complicated with sepsis. After 3 mo of hospitalization, the patient was discharged and continued outpatient follow up. Despite complete recovery of renal function and withdrawal of inflammatory syndrome, the patient felt unwell. He had headaches, was tired, cold intolerant, hypotensive, felt weak, apathic, and had decreased muscular strength. His appetite decreased and he vomited occasionally. Libido and facial, axillary, and pubic hair gradually decreased, and

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Table 1
Biochemical and Hormonal Characteristics of Three Patients with HFRS at Baseline

Parameter	Patient 1	Patient 2	Patient 3	Normal range
Cholesterol (mmol/L)	11.0	9.1	5.6	3.1–6.5
Triglyceride (mmol/L)	9.0	4.6	1.7	<1.95
Thyroxine (nmol/L)	26.6	43.3	—	55–160
FT4 (pmol/L)	—	—	2.79	9.8–16.8
TSH (mU/L)	1.7	1.55	1.57	0.15–5.0
Cortisol (nmol/L)	99.9	177.8	52.6	154–638
IGF-1 (ng/mL)	<25	61	<25	115–307
Growth hormone (peak to ITT, μg/L)	0.01	0.06	—	>3
Prolactin (mU/L)	91	47.0	99.8	90–370
Testosterone (nmol/L)	0.68	3.8	<0.5	8.2–34.6
FSH (IU/L)	0.1	2.6	0.87	1–10.5
LH (IU/L)	0.2	1.1	<0.85	1–8.4

he reported low sperm volume. He was married and fathered a child prior to HFRS. He was treated with statins without improvement in lipid levels.

On physical examination, he presented with dry skin, hypotension (100/70 mmHg), bradycardia, and loss of facial, pubic, and axillary hair. Testicular volume was 8 mL each.

The results (Table 1) revealed hypogonadotropic hypogonadism, low thyroxine level, and low cortisol concentration in the morning. Prolactin level was low-normal. There was no response of growth hormone, prolactin, and cortisol during an insulin tolerance test (ITT). Peak growth hormone concentration was less than 0.01 μg/L, and peak cortisol level was less than 200 nmol/L. IGF-I level was low. Magnetic resonance imaging showed empty sella with pituitary atrophy (Figs. 1A,B). Bone mineral density of the lumbar spine (DEXA) was normal. He was diagnosed hypopituitary and replaced with hydrocortisone, thyroxine, and testosterone. Following replacement, symptoms and lipids improved but did not normalize. Growth hormone deficiency was not replaced.

Case 2

A 45-yr old man was referred to our Institute for further endocrine evaluation of hyperlipidemia resistant to treatment with statins. Two years prior he was treated with hemodialysis due to acute renal failure caused by viral hemorrhagic fever. Serologic–immunofluorescence testing was positive for *Hantaan* (*Puumala*) virus (titer of specific antibodies was 1/2048). During hemodialysis therapy he had an episode of sepsis. After 2 mo of treatment he was discharged from the hospital and was followed as outpatient. Although the renal function recovered, hyperlipidemia persisted (Table 1). Despite the use of statins, lipid levels remained high.

On admission he had signs of hypothyroidism (bradycardia), and hypogonadism with testis 15 mL each. Baseline biochemical and hormonal characteristics are shown on Table 1. A stimulation test (ITT) showed no response of cortisol (peak cortisol level was 330 nmol/L), growth hormone, and prolactin. IGF-I level was low. Low T4 with normal TSH levels was found. Upon stimulation with TRH, TSH did not respond (peak TSH was 1.4 mU/L). Testosterone, FSH, and LH levels were low, without response to LHRH test. Magnetic resonance imaging again revealed an empty sella with atrophic pituitary gland, identical with the findings in the first patient. The diagnosis of hypopituitarsm was established and replacement therapy with hydrocortisone, L-thyroxine, and testosterone was begun. One month after replacement therapy, lipid levels improved.

Case 3

A 47-yr-old man was referred to us for further evaluation of hypogonadism. Two years prior he had HFRS with high titer of anti-*Puumala* virus antibodies. During the acute phase of illness he had myocardial infarction and cardiac arrest. In addition, dilatative cardiomyopathy developed. He was treated with hemodialysis and recovered. Soon after discharge from the hospital, he noticed total loss of libido and impotence associated with significant reduction in face and body hair. Simultaneously, he noticed dry skin and was cold intolerant. He had malaise and blood pressure was lower than usual (90/60 mmHg). Lipid levels were normal. Six months prior to admission he was evaluated for erectile dysfunction, and low levels of gonadotropins and testosterone were registered. Hormones at baseline are shown in Table 1. IGF-I level was low. Low FT4 with normal TSH levels was found, without increase of TSH upon stimulation with TRH (peak TSH was 2.0 mU/L). FSH and LH did not respond to stimulation with LHRH. Magnetic resonance imaging confirmed pituitary atrophy, similar to the findings in the previous two cases. Hydrocortisone, L-thyroxine, and testosterone replacement therapy was started. After 15 d of therapy, significant ECG improvement was observed and blood pressure normalized (120/80 mmHg).

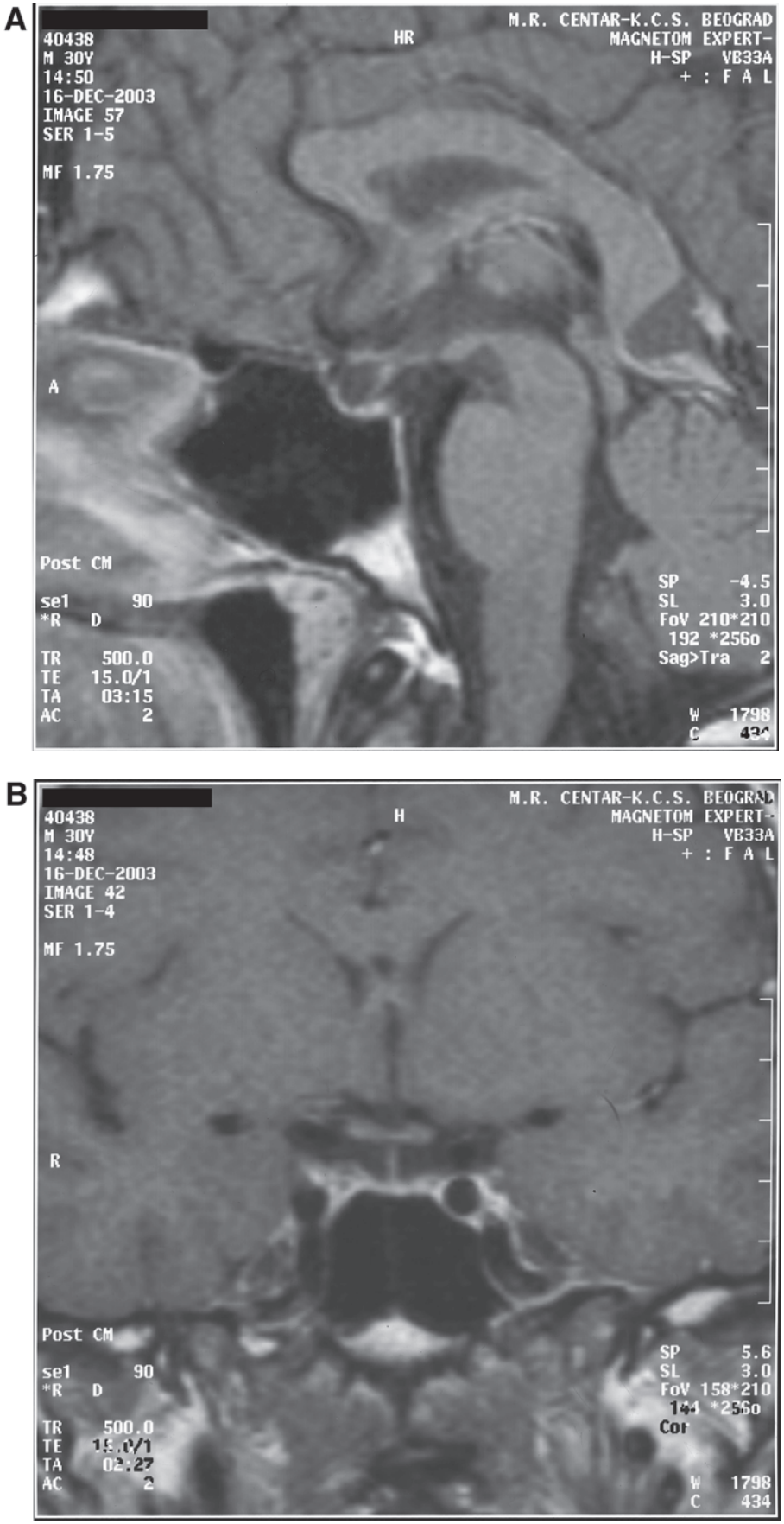

Fig. 1. Sagittal (**A**) and coronal (**B**) section on magnetic resonance scan showing an empty sella and atrophic pituitary gland in case 1.

Discussion

To the best of our knowledge, this is the first report of hypopituitarism that developed as a sequela of HFRS in the region of the Balkans where the disease is endemic and occurs either sporadically or in epidemics (the last one was in 1995). All three patients fully recovered renal function after severe forms of HFRS, which they suffered 2 yr ago, while pituitary failure remained undiagnosed.

Hypopituitarism may be mild, moderate, or severe. Mild hypopituitarism can remain undetected for many years with concomitant development of metabolic syndrome, as in our two patients. Nowadays, a pituitary tumor is the most common cause of acquired hypopituitarism, while ischemic infarction and necrosis of the pituitary gland (Sheehan syndrome) is a rare cause *(15)*. In 1914, Simmonds described autopsy findings in a 46-yr-old woman who died from chronic hypopituitarism as a consequence of severe puerperal sepsis 11 yr earlier *(16)*. At autopsy, her pituitary gland was severely atrophied and was replaced by a fibrous scar. The cause was bacterial emboli. In 1937, Sheehan postulated that pituitary necrosis may be caused by ischemia/infarction, rather than by puerperal sepsis or mycotic/bacterial emboli *(17)*. Pituitary necrosis unrelated to postpartum ischemic infarction occurs in other pathological situations: raised intracranial pressure, damage to the pituitary stalk, acute pituitary apoplexy, accidental trauma (traumatic brain injury), massive stroke, and subarrachnoid hemorrhage. Increased incidence of pituitary necrosis has also been reported in patients with diabetes mellitus, in patients after cardiac surgery, and in patients on assisted ventilation and in acute hemorrhagic fever as was the case in our patients *(18)*. Normal pituitary function can be supported by about 50% of the pituitary gland, while partial and total hypopituitarism are accompanied by loss of 75% and 90% (respectively) of the pituitary gland *(18)*.

The anterior pituitary gland is one of the most common sites of hemorrhage in HFRS together with the renal medulla and the right atrium of the heart, possibly because of its anatomical localization and organization of blood supply *(19,20)*. The anterior lobe of the pituitary gland receives only 10–20% of its blood supply from superior and inferior hypophyseal arteries, while the remaining 80–90% is provided by hypophyseal venous portal circulation. The mechanism of hemorrhage and necrosis of the pituitary gland is still unknown, but vasospasm accompanied by shock is suggested. There is no evidence of vascular occlusion *(19)*. Hantaviruses specifically infect endothelial cells and interact with β-3 integrins presented on platelets *(13)*. The central physiologic derangements in HFRS and the causes of hemorrhage are increased vascular permeability, thrombocytopenia, and platelet dysfunction.

Since Mayer described the clinically manifested hypopituitarism following HFRS, a few more case reports have been documented *(12–14,21)*. The analysis of lethal outcomes of HFRS showed the occurrence of hemorrhage and necrosis in the anterior lobe of the pituitary gland to be present in 50–100% of cases *(19,20,22)*. These data are in agreement with Lee and van der Groen who described necrosis and hemorrhage in the anterior lobe of the pituitary gland in 60% of patients who died during the hypotensive phase of HFRS, and in almost all patients who died during the oliguric phase of the disease *(23)*. The atrophic changes in the pituitary seen on the MRI imaging in our patients are similar to those described in other reports showing progressive pituitary atrophy *(12,14)*. It is possible that hypopituitarism is more common than is recognized, and that it should be considered in any case of severe HFRS.

In conclusion, we presented three patients who developed hypopituitarism as a complication of severe HFRS. Pituitary failure is rarely considered in patients who survive HFRS. Our patients demonstrate the importance of investigating the endocrine status in all survivors of severe forms of HFRS. The clinical course of the hypopituitarism in our patients was chronic and undiagnosed for a long period until the metabolic syndrome and hypogonadism became overt.

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