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Panhypopituitarism and Central Diabetes Insipidus as a Complication of Hemorrhagic Fever with Renal Syndrome (Korean Hemorrhagic Fever)†

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= Abstract =Panhypopituitarism and diabetes insipidus of the central type developed in a 32-year-old male patient with hemorrhagic fever with renal syndrome confirmed by indirect immunofluorescent test.

Visual disturbance, loss of consciousness and neck stiffness developed during the early course of the illness followed by persistent polyuria. Combined anterior pituitary function tests showed no response in all anterior pituitary hormones. The sella CT illustrated the features of a partial empty sella. Diagnosis of diabetes insipidus was based on water deprivation and pitressin tests.

Although pituitary necrosis was observed almost in all cases of hemorrhagic fever with renal syndrome at autopsy, 10 reports dealt with cases complicated by panhypopituitarism. To our knowlege, no case of central diabetes insipidus as a complication has been reported yet, so this seems to be the first.

Key Words : ***Hemorrhagic fever with renal syndrome, Diabetes insipidus, Panhypopituitarism***

INTRODUCTION

Hemorrhagic fever with renal syndrome (HFRS, Korean hemorrhagic fever) is an acute illness characterized by fever, bleeding tendencies, hypotension and renal insufficiency and is known to result in few sequelae on recovery.

Although pituitary necrosis is observed in almost all autopsy cases (Kim 1972), and up to 77 % of sella CT shows abnormal findings in HFRS (Chang *et al.* 1984), there are few reports on anterior pituitary dysfunction as a complication. In particular, central diabetes insipidus caused by HFRS has not been clearly documented in the literature despite infrequent association of prolonged defects in urine concentration.

We report a patient with HFRS complicated by central diabetes insipidus and anterior pituitary failure.

CASE REPORT

A 32-year-old man was referred to the Seoul National University Hospital because of oliguria and impaired consciousness. He was well until 11 days ago when fever, chill, headache, myalgia and facial flushing developed. Two days later, nausea, vomiting, and abdominal pain appeared followed by blurred vision. On the third day of his illness, he was admitted to another hospital. His temperature was 39.4°C. Conjunctival injection and petechiae on the soft palate and axillae were noted. On the

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day after admission, the BP fell to 70/40 mmHg and the urine output dropped to 30 ml/day. The impression was HFRS in oliguric phase and peritoneal dialysis was started, but he was transferred to Seoul National University Hospital because of decreasing consciousness. He became confused on the 6th day of illness, and on the 7th day seizure developed. Five days later, he became stuporous and ankle clonus developed.

He lived at Euijungboo, an endemic area of this disease near Seoul. He participated in army reserve military field exercises 10 and 15 days prior to onset of symptoms.

On examination, he was an acutely ill-looking, slightly dehydrated man. Blood pressure was 100/80 mmHg, pulse rate 80/min, respiratory rate 24/min and temperature 36.7°C. Blood clots in the oral cavity and petechiae on the soft palate were found. There was diffuse abdominal tenderness, and rebound tenderness with hypoactive bowel sounds. Bloody stool was determined on rectal examination. There were petechiae on the axillae, and ecchymoses and purpura over multiple sites of his upper extremities, both shoulders and buttocks. Neurologic examination showed a semicomatous man. The pupils were isocoric and constricted. The light reflex was consensual but sluggish. No patho-

Table 1. Laboratory findings on admission (13th day of illness)

CBC	Hb 7.5 g/dl, Hct 23 %, WBC 7,600/mm^3 (stab 1, seg 91, lympho 4, mono 2, myelo 2 %) Platelet 35,000/mm^3
Bleeding	BT 7′, PT 14″(58%), aPTT 33″ Fibrinogen 500 mg/dl, FDP 40 μg/ml
Urine	amber cloudy, pH 7.5, SG 1.010, Alb 2+, Blood 3+ RBC many/HPF, WBC 5-7/HPF
Renal Function	BUN 180 mg/dl, Creatinine 14.2 mg/dl
Electrolyte	Na 124 mEq/L, K 4.8 mEq/L, Cl 92mEq/L, Ca 4.9mg/dl, P 9.4mg/dl
Chemistry	Protein 5.6g/dl, Albumin 2.0g/dl, Bilirubin(total) 0.8 mg/dl, Alk.P'tase 145 IU/L, SGOT 42 IU/L, SGPT 8 IU/L
Lipid	Cholesterol 105 mg/dl, Triglyceride 178 mg/dl, HDL-Cholesterol 10 mg/dl
Serology	ASO negative, CRP 6+, RA negative, Cryoglobulin negative, VDRL negative IgG 1900 mg/dl, IgA 162 mg/dl, IgM 116 mg/dl
Immunology	C3 98.2 mg/dl, C4 42.3 mg/dl, CH50 56.3U/dl
Antibody to Hantaan virus	2+(6th D), 4+(13th D), 4+(30th D)

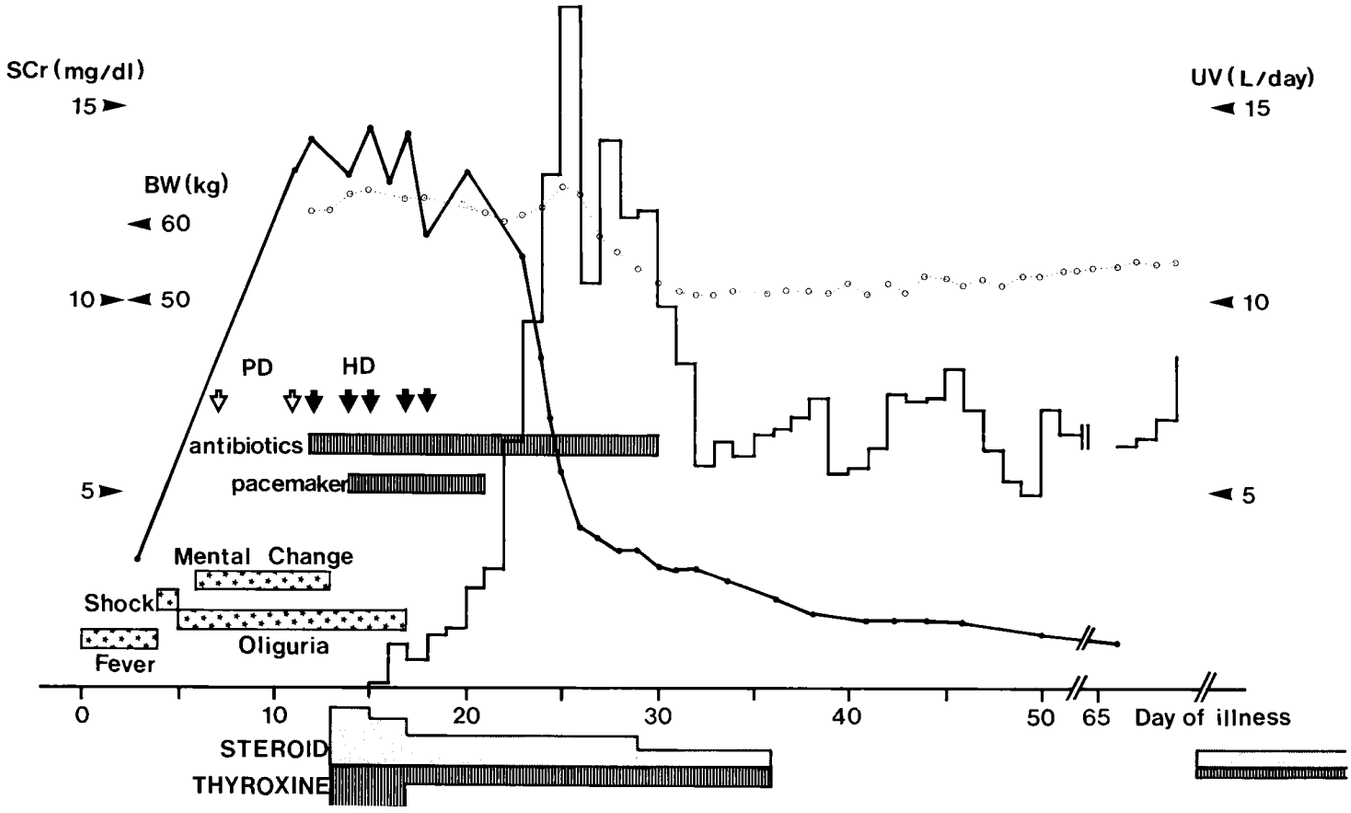

Fig. 1. Clinical course of the presented patient.

logic reflexes except ankle clonus were noted. There was neck stiffness (Fig. 1).

Laboratory findings on admission are summarized in Table 1. Basal hormone levels on the 13th day of illness were as follows. The prolactin was 8.1 ng/ml, cortisol 1.8 μg/dl and the TSH 1.6 μ U/L. The T3 RU was 23.7 %, T3 RIA and T4 levels were less than 25 ng/dl and 1.0 μg/dl, respectively.

Combined anterior pituitary function tests using intravenous administration of TRH 400 μg, LHRH 100 μg and regular insulin 6 u was done on the 20th day of illness after discontinuing drugs for 31 days. The results showed loss of anterior pituitary reserve (Table 2). 24 hour urinary 17-KS and 17-OHCS measured on the 67th day of illness were 7.3mg and 1.0mg, and those on 158th day of illness were 2.4mg and 2.3mg per day.

The sella CT image was obtained by serial scanning with 1.5mm thickness and 1.5mm intervals after intravenous injection of contrast material on the 19th day of illness. Downward displacement of the superior margin of the sella with the features of partial empty sella was observed. A repeat scan was performed on the 66th day of illness and the above findings became more evident suggesting progressive pituitary atrophy (Fig. 2).

To evaluate the cause of polyuria which persisted

Table 2. Results of combined anterior pituitary function test

Date	May 20, 1895						July 6, 1985					
Day of illness*	20**						67***					
Hormone \ Time	Basal	15	30	60	90	120	Basal	15	30	60	90	120
Glucose	105	70	55	80	105	90	60	2502†	50	50		
GH	<1.0			<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0		
Cortisol	19.2			14.8	12.3	<1.0	1.5	<1.0	1.9	3.2		
Prolactin	1.0	<5	<5	<5		<5	<5	<5	<5	<5		
TSH	11.2	1.0	1.0	1.0		1.0	1.0	1.0	1.0	1.0		
LH	1.4		16.8	15.5	16.5	5.8	4.2	6.4	5.0	3.7		
FSH			3.1	2.7	1.9	1.7	2.0	1.8	2.2	2.4		

*:calculated from the onset of fever

**:hydrocortisone 30 mg & levothyroxine 10 μg/day

***:No medication since 36th day of illness

†:50% glucose 50 ml was infused intravenously

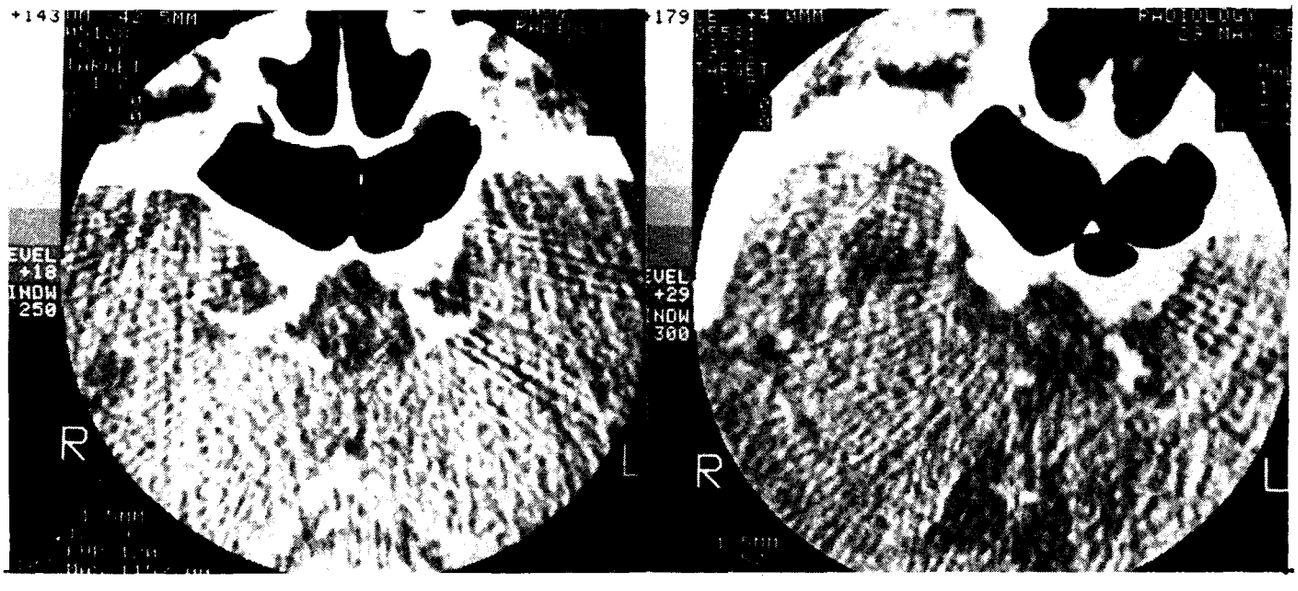

Fig. 2. Sella CT showing partial empty sella (Rt on 29th and Lt on 66th day of illness).

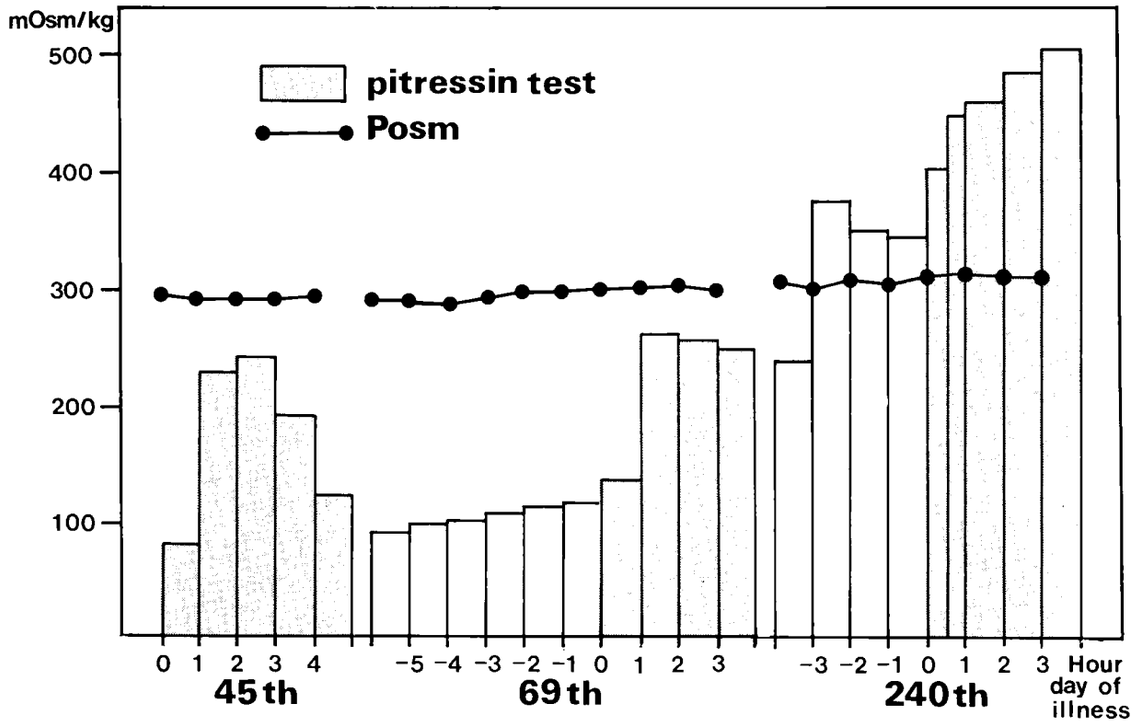

Fig. 3. Water deprivation and pitressin test results.

in spite of fluid restriction, water deprivation and pitressin tests were carried out. In the pitressin test, 5u aqueous pitressin was administered subcutaneously. The response to water deprivation was negligible. In response to the pitressin injection urine osmolality increased to 186% on the 45th day of illness and to 93% on the 69th day of illness. The percent increment of urine osmolality was only 25% on the 240th day of illness, when it was noted that the pitressin requirement was reduced (Fig. 3).

Pituitary apoplexy was managed with large intravenous dose of hydrocortisone and thyroxine, which were gradually switched to oral prednisolone 7.5 mg/day and levothyroxine 100 μg/day. For diabetes insipidus, nasal Desmopressin was used but because of nasal irritation, pitressin tannate in oil was substituted from the 115th day of illness. The initial dose of pitressin was 5 μ/48 h, but about 3 months later, a slight decrease in the requirement was noted. He remains well on 5 μ/60h since the 240th day of illness.

COMMENT

The patient is a classical case of HFRS from both clinical and laboratory points of view. The panhypopituitarism in this patient was due to HFRS, since other causes than HFRS were easily excluded by history or laboratory tests. Hormonal imbalance caused by acute renal failure could also be eliminated, because in acute renal failure, basal prolactin and growth hormone levels should be high with exaggerated response to stimulation. Moreover, the LH level is not low in acute renal failure, and these abnormalities usually return to normal after recovery of renal function (Massry *et al.* 1983).

Anterior pituitary failure complicated by HFRS was first suggested by Mayer (1952) and about 10 reports are known in the literature (Zoeckler and Orbison 1955; Kim 1965; Klebanov 1976; Kim *et al.* 1977; Cho *et al.* 1979; Song *et al.* 1981; Lee 1985). Among these only 3 are documented by hormone assay (Kim *et al.* 1977; Song *et al.* 1981; Lee 1985). Some of these cases were detected several months or years after the onset of HFRS, while some presented as pituitary apoplexy as shown in this patient.

The pathologic findings of the pituitary gland in HFRS coincides with hypopituitarism as a complication, because a unique coagulation necrosis involving more than 90% of the anterior pituitary gland area is found in one-third of autopsy cases (Kim 1972). The mechanism of pituitary necrosis has not been fully established yet. Inferring from clinical and pathologic findings, the pathogenesis could be summarized as anoxic damage to gland highly susceptible to hypoxic injury because of the

nature of its vasculature. It might result from vascular insufficiency due to the combined effects of congestion, stasis, high viscosity, thrombotic occlusion secondary to the disseminated intravascular coagulation, and vessel compression with the swelling of the gland in a limited space of sella turcica (Lee 1985). The contribution of hypotension or vasoconstriction should be considered also.

The explanation for the discrepancy in prevalence between the clinical and morphologic involvements of the anterior pituitary gland may be inferred from the fact that the survivor has a milder lesion than the patient who dies. Another possibility may be the lack of diagnostic suspicion, because the symptoms of pituitary apoplexy are often overlooked as the symptoms of HFRS itself (Klebanov 1976). Therefore one should check the anterior pituitary function in circumstances of panhypopituitarism or when an empty sella is detected, especially in men in the endemic area. Weakness and malaise persist long after the convalescent phase of HFRS, and CNS manifestations such as loss of consciousness, seizure and visual disturbance develop during the acute phase.

Diabetes insipidus is accompanied by pituitary apoplexy in 23% (Veldhuis and Hammond 1980). In Sheehan's syndrome, a disease with similar pathology and mechanism in pituitary gland damage, there are more than 30 cases of diabetes insipidus reported. For HFRS, especially for a case supposedly complicated by diabetes insipidus, as mentioned by Zoeckler and Orbison (1955), the authors were not able to discover any confirmed case, though the prolonged defect in urinary concentration has been frequently described (Lee 1969).

The usual pathologic findings of the posterior pituitary gland include mild congestion, hemorrhage and focal cell infiltration only. In severe cases, the stalk is damaged by the extension of anterior pituitary hemorrhage, which is replaced by the fibrous connective tissues (Wahle and Mckay 1953). These findings are not different from those of Sheehan's syndrome. According to the descriptions of Sheehan and Whitehead (1963), stasis, hemorrhage or thrombosis are observed in stalk vasculature with little change in the neurohypophysis in early phases. Later, neurohypophyseal scarring and atrophy are the outstanding findings. These are related to neuronal loss in supraoptic or paraventricular nuclei rather than to the previously observed minute lesions of the posterior gland. On the other hand, it is proved that the neurohypophyseal injury to the stalk or hypothalamus by animal experiments (Heinbecker and White 1981). Therefore the lesions of the stalk or hypothalamus produce diabetes insipidus in pituitary apoplexy in the early phase. Spontaneous partial recovery in this case also shows a supportive finding of stalk or suprasellar insult.

Combined nephrogenic diabetes insipidus should be considered, and ADH level would be of help if it is measured. Glucocorticoid deficiency secondary to anterior pituitary failure may mask diabetes insipidus by defects in water excretion. This association should be born in mind when managing the fluid balance or replacing glucocorticoides in HFRS.

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= 국문초록 =

신증후출혈열(한국형출혈열)에 병발된 뇌하수체 전·후엽 기능부전증

서울대학교 의과대학 內科學敎室 및 病理學敎室*

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저자들은 간접면역형광법으로 진단된 신증후출혈열 환자에게 범뇌하수체 기능부전증과 중추성요붕증이 병발된 증례를 경험하였다.

환자는 32세 남자로서 핍뇨기 경과중에 시력이상, 의식소실, 경부강직을 보였고 이뇨기 이후 3개월 이상 1일뇨량 5*l* 이상의 요농축장애가 지속되었다. 뇌하수체 복합자극검사상 기능부전의 소견을 보였고, 수분박탈검사와 pitressin 반응검사 결과 중추성임을 확인하였으며, 병력, 이학적 소견, 뇌전산단층촬영 등 제검사 소견으로 미루어 볼 때, 다른 원인에 의해 유발되었을 가능성은 배제할 수 있었다.

뇌하수체 전엽의 괴사는 핍뇨기 이후 거의 전례에서 관찰되고 있으나, 실제 임상례로 증명된 경우는 매우 드물고, hormone assay로 확인된 보고는 3편에 불과하다. 한편 신증후출혈열에 병발된 중추성 요붕증에 대하여 저자가 문헌검토한 바에 의하면 아직 알려진 바 없어서, 본 증례가 처음인 것으로 사료된다.

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