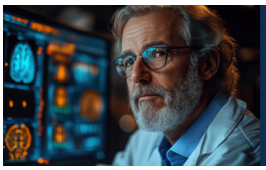

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T H Lim, K H Chang, M C Han, Y B Chang, S M Lim, Y S Yu, Y H Chun and J S Lee

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Pituitary Atrophy in Korean (Epidemic) Hemorrhagic Fever: CT Correlation with Pituitary Function and Visual Field

Tae Hwan Lim[1]
Kee Hyun Chang[2]
Man Chung Han[2]
Yun Bok Chang[3]
Sang Moo Lim[3]
Young Suk Yu[4]
Young Hwan Chun[1]
Jung Sang Lee[5]

Eleven patients with Korean (epidemic) hemorrhagic fever were each studied three times with high-resolution CT in order to demonstrate necrosis of the pituitary gland and to correlate the CT findings with the patients' pituitary function and visual fields. Seven of the 11 patients showed varying degrees of progressive decrease in the height of the pituitary gland: one severe, two moderate, and four mild. The visual fields of all the patients were checked at the time of the third (last) follow-up CT. Six of the 11 patients had bitemporal superior quadrantanopsia. In five patients, the decreased height (atrophic change) of the pituitary gland and the visual-field defect were coincidental. The visual-field defects in those patients were not improved on follow-up examination 5 weeks later. Two patients in whom a 1-year follow-up examination was performed showed no interval changes in the defects. Pituitary function tests were performed in nine of the 11 patients (six with atrophic pituitary glands and three without atrophic changes) at the time of the third CT. Five of the six patients with atrophy showed decreased pituitary reserve function for follicle-stimulating hormone, cortisol, or human growth hormone, while only one patient showed decreased reserve function for cortisol among the three patients without atrophic change. The pituitary atrophic changes observed on follow-up sellar CT are thought to be the result of the ischemic necrosis of the gland. The high probability (five of seven) of visual-field defects in those patients with atrophic glands suggests optochiasmatic and pituitary ischemia as the basic pathogenesis.

Korean hemorrhagic fever (KHF), more commonly known in the Western world as epidemic hemorrhagic fever, is a viral infectious disease that is endemic on the Korean peninsula. The disease is known to have common antigenicity with the epidemic hemorrhagic fever of Japan [1] and the nephropathia epidemica of Scandinavia [2], and it is thought to be virtually the same disease as the "hemorrhagic fever with renal syndrome" [3] of the USSR, China, and Eastern Europe.

Clinically, the disease is known to have five phases: febrile, hypotensive, oliguric, diuretic, and convalescent. It is characterized by a pathologic triad consisting of congestion and hemorrhage in renal medulla, hemorrhage in right atrial wall, and necrosis of the anterior lobe of the pituitary gland [4–8]. To our knowledge, there have been no reports of radiologic studies demonstrating the changes of the pituitary gland in KHF.

We performed sequential high-resolution CT three times each on 11 patients who had KHF in order to observe the morphologic changes of the pituitary gland in vivo and to correlate the CT findings with the results of the pituitary function tests and visual-field examinations.

Materials and Methods

We examined 11 patients with KHF who were admitted to the Capital Armed Forces General Hospital, Seoul, Korea, during a 4-month period. The patients were all men ranging in age from 20 to 30 years.

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[1] Department of Radiology, Capital Armed Forces General Hospital, Seoul, Korea.

[2] Department of Radiology, College of Medicine, Seoul National University, #28 Yeongun-Dong, Chongno-Ku, Seoul 110, Korea. Address reprint requests to M. C. Han.

[3] Department of Internal Medicine, Capital Armed Forces General Hospital, Seoul, Korea.

[4] Department of Ophthalmology, Capital Armed Forces General Hospital, Seoul, Korea.

[5] Department of Internal Medicine, College of Medicine, Seoul National University, Seoul, Korea.

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Three high-resolution CT scans of the sella were obtained on each of the patients: (1) first CT 3–5 days after onset (in the febrile, hypotensive, or oliguric phase); (2) second CT 2–3 weeks after onset (in diuretic phase); and (3) third CT 7–11 weeks after onset (in convalescent phase). Informed consent was obtained for each examination. Although KHF has five phases, the first three often overlap, and occasionally the hypotensive and/or oliguric phases are missing.

All scans were performed on a Technicare (Solon, OH) 2020 scanner using 120 kVp and 800 mAs with a scanning time of 8 sec. The slice thickness and scanning interval were 2 mm. Coronal as well as axial scannings were performed, and sagittal reconstruction images were obtained from the transverse scans in all patients. The coronal scanning was done perpendicular to the inferior orbitomeatal line; the axial scans parallel to that line. Only postcontrast CT images were obtained (100 ml bolus of Conray 60% [iothalamate meglumine VSP 60%, Mallinckrodt, St. Louis, MO] followed by a drip infusion of 50 ml during the scanning for a total iodine content of 42.3 g). Since pituitary necrosis is known to occur most commonly in the anterior lobe of the pituitary gland in KHF, the height of the pituitary gland and the depth of the sella were measured in the midline in the region of the anterior lobe; that is, just anterior to the section that showed the infundibular stalk most clearly. The presence or degree of the pituitary atrophy was determined by the degree of cisternal herniation (modified from Roppolo's method [9]: "normal," up to 25% herniation; "mild," 25–50%; "moderate," 50–75%; and "severe," 75–100% (Fig. 1).

In all patients, visual fields were checked in the convalescent phase at the time of the third CT, using the Goldmann perimeter [10]. Five weeks later, we reexamined the patients who had visual-field defects. In two patients, we performed a 1-year follow-up check with a tangent screen using a red color target.

In nine of the 11 patients, pituitary function tests were performed at the time of the third CT. Basal levels and responses to the stimulation test for follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), human growth hormone (HGH), cortisol, and prolactin were measured. We used the Amerlex RIA Kit (Amersham, UK) for FSH, LH, cortisol, and prolactin; the HGH Kit (Serono, Braintree, MA) for HGH; and HTSH RIABEAD (Abbott, Chicago, IL) for TSH.

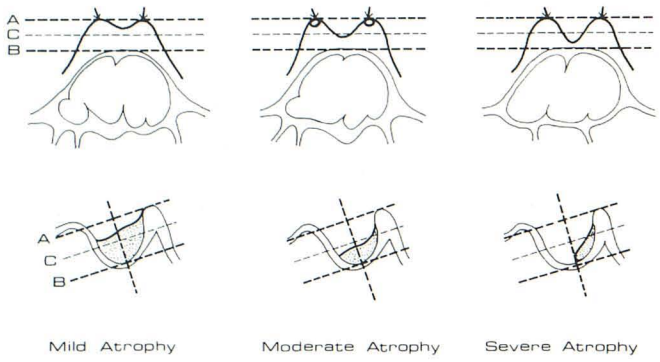

Fig. 1.—Determination of degree of pituitary atrophy. Mild atrophy corresponds to 50% of cisternal herniation; moderate, 50–75%; severe, 75–100%. **A**, Level of superior border of sella turcica. *Arrows* indicate points of juncture of cavernous sinuses or anterior clinoid processes with diaphragm sella. **B**, Level of floor of sella turcica. **C**, 50% line of line A and B. Cisternal herniation = (AB − height of gland/AB).

Results

On the initial CT, the size and shape of the pituitary gland were normal in all 11 patients. The superior surface of the gland was flat in six patients and slightly convex in five; the mean gland height was 4.5 ± 0.50 mm at the region of the anterior lobe.

On the second CT, five of the 11 patients had mild atrophic changes of the gland. The remaining six patients showed no interval changes during the period between the first and second CT. In two of the five patients who had mild atrophic change of the gland on the second CT, there was progression of the atrophy on the third CT; one showed severe atrophy with nearly total loss of the gland tissue (Fig. 2C) while the other showed moderate atrophy (Fig. 3C). In the remaining three patients with mild atrophy on the second CT, no interval change was seen on the third CT (Fig. 4).

In two of the six patients who did not show atrophic changes on the first and second CTs, the gland became atrophic on the third CT—one mild and the other moderate. In four patients the size and shape of the gland remained normal throughout all phases of the disease. The sequential

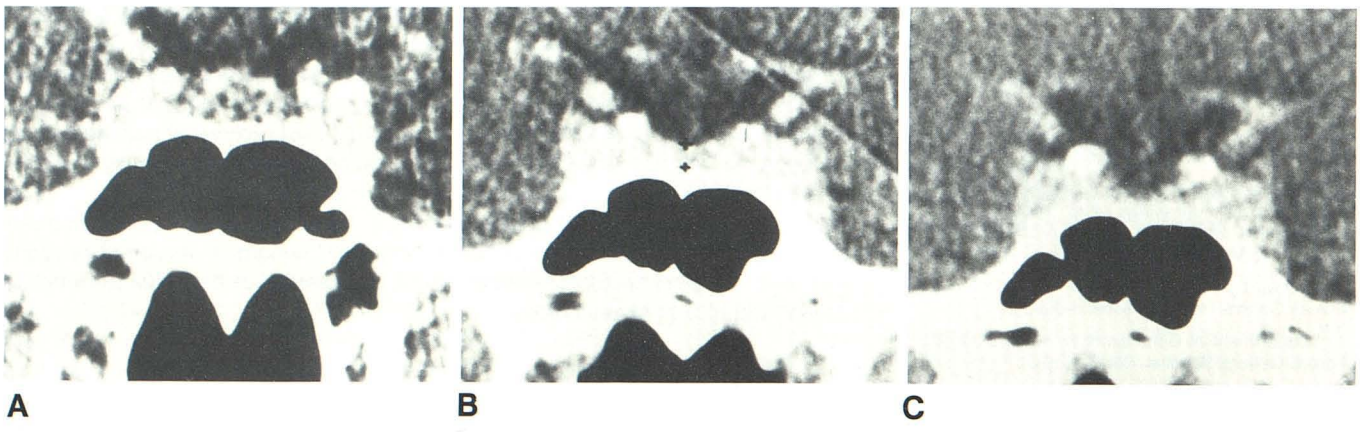

Fig. 2.—Case 1. Sequential coronal CT of sella showing severe progressive atrophic change of the pituitary gland. **A**, First CT (normal pituitary gland). **B**, Second CT (mild atrophy). **C**, Third CT (severe atrophy; region of anterior lobe is nearly "empty" and replaced by CSF density).

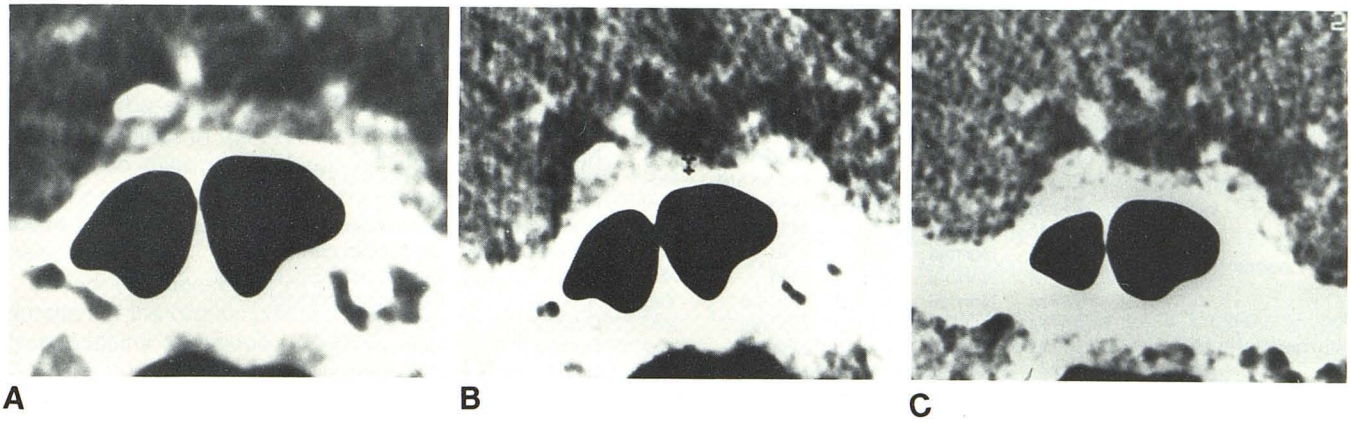

Fig. 3.—Case 3. Moderate degree of progressive pituitary atrophy. **A**, First CT (normal pituitary). **B**, Second CT (mild atrophy). **C**, Third CT (moderate atrophy). Small cystic low density within left side of enhanced sellar area on **C** is an artifact.

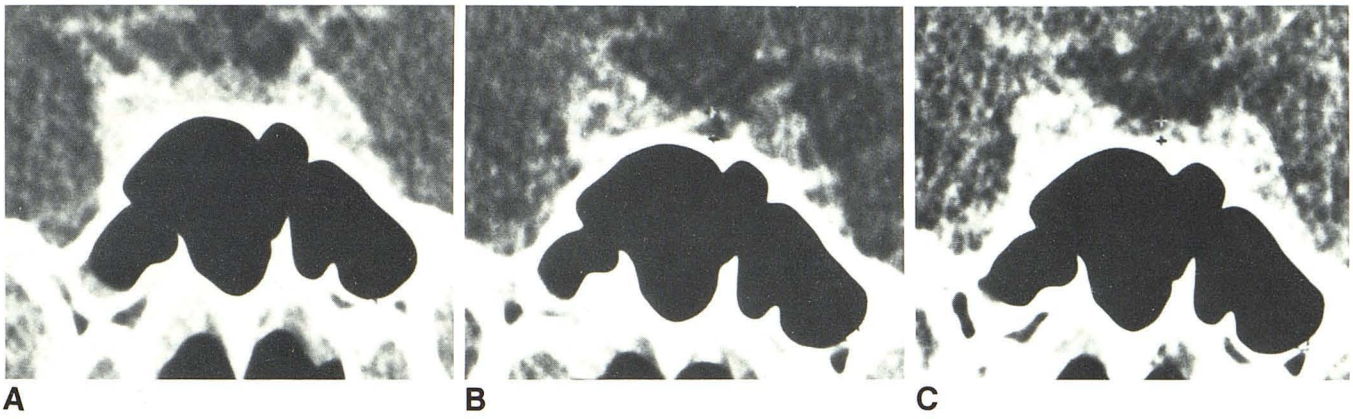

Fig. 4.—Case 7. Mild degree of progressive pituitary atrophy. **A**, First CT (normal pituitary). **B**, Second CT (mild atrophy). **C**, Third CT (mild atrophy). Round low density within enhanced sellar area on **B** is an artifact.

TABLE 1: **Sequential Change of Height of Anterior Lobe of Pituitary Gland**

Type of Patient	No. of Patients	Height of Anterior Lobe of Pituitary Gland (mm)		
		First CT[a]	Second CT[b]	Third CT[c]
With pituitary atrophy	7	4.6 ± 0.50	3.3 ± 0.45	2.0 ± 0.53
Without pituitary atrophy	4	4.3 ± 0.44	4.3 ± 0.44	4.3 ± 0.44

[a] First CT was performed in febrile, hypotensive, or oliguric phase.
[b] Follow-up CT in diuretic phase.
[c] Follow-up CT in convalescent phase.

changes in the height of the gland are summarized in Table 1.

Six of the 11 patients had bitemporal superior quadrantanopsia. Among the seven patients who showed atrophy of the pituitary gland on CT, five had visual-field defects. Among the four patients without pituitary changes, only one had a visual-field defect (Table 2). These visual-field defects did not improve or worsen on follow-up examination performed 5 weeks later. In two patients a 1-year follow-up examination revealed no improvement of the bitemporal superior quandrantanopsia.

Six of the nine patients on whom pituitary function tests were performed showed a decreased pituitary reserve function for FSH, HGH, or cortisol. Five of those patients had atrophic changes of the pituitary gland. The basal levels of each hormone were normal in all patients except one, who showed elevation of FSH level (Table 2).

Discussion

Clinically, KHF is characterized by sequential phases: febrile, hypotensive, oliguric, diuretic, and convalescent. The febrile phase begins with sudden high fever, chills, headache, myalgia, back pain, dizziness, and general weakness, and lasts 4–6 days. Two or three days after onset of the illness, gastrointesinal symptoms such as anorexia, nausea, vomiting, and abnormal pain develop. Early physical signs are facial flushing, facial edema, proptosis, conjunctival injection, con-

TABLE 2: **Summary of Sellar CT, Visual Field, and Pituitary Function Test**

Case No.	Age Gender	Degree of Pituitary Atrophy			Visual Field Defect[d]	Pituitary Function Test[e]	
		First CT[a]	Second CT[b]	Third CT[c]		Basal Level	Stimulation Test
1	23, M	Normal	Mild	Severe	Yes	Normal	Decreased FSH, HGH
2	22, M	Normal	Normal	Moderate	Yes	Normal	Normal
3	20, M	Normal	Mild	Moderate	No	Normal	Decreased FSH
4	21, M	Normal	Normal	Mild	Yes	Not done	Not done
5	21, M	Normal	Mild	Mild	Yes	Normal	Decreased cortisol
6	23, M	Normal	Mild	Mild	Yes	Increased FSH	Decreased cortisol
7	22, M	Normal	Mild	Mild	No	Normal	Decreased FSH, cortisol
8	24, M	Normal	Normal	Normal	Yes	Normal	Decreased cortisol
9	23, M	Normal	Normal	Normal	No	Normal	Normal
10	21, M	Normal	Normal	Normal	No	Normal	Normal
11	24, M	Normal	Normal	Normal	No	Not done	Not done

[a] First CT was performed in febrile, hypotensive, or oliguric phase.
[b] Follow-up CT in diuretic phase.
[c] Follow-up CT in convalescent phase.
[d] All were bitemporal superior quadrantanopsia.
[e] Serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), human growth hormone (HGH), cortisol, and prolactin were checked.

junctival edema, lymph node enlargement, and tenderness at the costovertebral angles. Petechia usually develops after the third day and is most prominent on the soft palate, axilla, chest wall, and face. The febrile phase is seen in 100% of patients. The hypotensive phase is seen in 45–48% of patients, develops abruptly in the late febrile phase, and lasts for a few hours to 3 days.

The oliguric phase is seen in 48–66% of patients and begins during the febrile or hypotensive phase, lasting 3–6 days. Symptoms of the febrile phase disappear in this phase, and frequently the accompanying uremic symptoms necessitate peritoneal dialysis or hemodialysis.

The diuretic phase starts with sudden increase in urine output to 1000–2000 ml/day, eventually increasing to 3000–6000 ml/day. In extreme cases, the urine output is over 10,000 ml/day. Ninety to 95% of patients go through this phase, which lasts for several weeks. The convalescent phase begins 1 or 2 months after the diuretic phase, and the urinary output then decreases to 2000 ml/day [11].

The etiologic agent of KHF is a spherically shaped virus with 75 ± 5 nm diameter and 52 doughnut-shaped surface processes that are known to have specific antigenicity [12]. This virus is called the "Hantaan virus" after the river of the same name that traverses the most endemic region of Korea [13, 14].

Hullinghorst [4] and Lukes [5] reported that between 72–76% of their autopsy cases of KHF revealed necrosis of the anterior lobe of the pituitary gland, and that almost all the patients who died after the ninth day of the disease had necrosis. According to Steer [6], the presence and severity of foci of necrosis in the anterior lobe of the pituitary gland appeared related to the phase of the disease at the time of death. Approximately 58% of their patients who died in the hypotensive phase had mild pituitary necrosis, whereas all their patients who died in the oliguric phase had severe pituitary necrosis.

In our study, seven of the 11 patients (64%) showed progressive decrease of the pituitary gland height, indicating atrophic change or necrosis of the pituitary gland. This incidence is slightly lower than that seen on autopsy studies, but is greater than the incidence of clinically detected hypopituitarism complicating KHF. Although five of six tested patients with pituitary atrophy had decreased reserve function for FSH, HGH, or cortisol, the basal hormone levels were not decreased, even in the patients who showed over 50% atrophy of the gland tissue. Even in severe cases, pituitary atrophy does not necessarily result in hypofunction of the gland.

Although autopsy studies show a high incidence of pituitary necrosis, hypopituitarism rarely develops in the clinical course of KHF [15–17]. In a clinical study, Lee et al. [18] recently reported that 10–43% of their patients showed transiently decreased pituitary reserve function for various hormones. These results suggest that there are many patients who undergo subclinical hypopituitarism.

In our study, five of the six patients with visual-field defects showed atrophic changes of the pituitary gland, and these field defects are thought to be the basis of optochiasmic ischemia. These ischemic changes can occur after surgery or radiation therapy for pituitary or parasellar tumors. There are also reports of chiasmal syndrome associated with primary empty sella syndrome [19]. Lee et al. [20–21] categorized the chiasmal syndrome (mainly bitemporal hemianopsia) of nonneoplastic origin. Twenty-five of their 30 cases were associated with an empty sella, and they proposed an optochiasmatic ischemia as the common pathologic basis of the chiasmal syndrome and the empty sella syndrome. All of their patients who had the chiasmal syndrome associated with the postpartum pituitary necrosis showed an empty sella, and they slowly recovered from the chiasmal syndrome. In our cases, the visual-field defects were all bitemporal superior quadrantanopsias. The inferior surface of the optic chiasm and the anterior lobe of the pituitary gland have a common blood supply, mainly from the anterior superior hypophyseal artery [20, 22]. The necrosis of the anterior lobe of the pituitary gland and the visual-field defect in KHF seem to have the same pathogenesis; that is, ischemia. In fact, recent

available evidence suggests that thrombus formation from disseminated intravascular coagulation and vascular compression by edema and hematoma are the probable pathologic bases for ischemic necrosis of the pituitary gland [23]. In contrast to the cases reported by Lee et al. [20–21] of ischemic chiasmal syndrome associated with postpartum pituitary necrosis, our two patients who underwent a 1-year follow-up examination did not recover from the visual-field defects.

The clinical severity of KHF is usually determined by the duration of the oliguric phase and by the occurrence of such complications as anemia, bleeding, ascites, and pulmonary edema. Of our 11 patients, six had undergone 4–8 days of oliguric phase (400 ml/day or less urine). Of these six patients, five (83.3%) had pituitary atrophy on CT and four (66.7%) had visual-field defects. Among the five patients without an oliguric phase, two (40%) had visual-field defects. The frequency of pituitary necrosis and visual-field defects seems to be higher in patients undergoing a severe clinical course.

In summary, of 11 patients with KHF we observed varying degrees of pituitary atrophy on follow-up CT in seven (63.6%) and visual-field defects (bitemporal superior quadrantanopsia) in six (54.5%). There was a high rate (71.4%) of visual-field defects in those patients with pituitary atrophy. The patients with an atrophic gland showed a high probability of decreased pituitary reserve function for various hormones, such as FSH, cortisol, or HGH. We recommend sellar CT and visual-field examinations in patients with KHP in order to determine the presence and degree of pituitary atrophy and visual-field defects.

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