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# CT of the Pituitary Gland in Multiple Endocrine Neoplasia Type 1 Syndrome

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**Multiple endocrine neoplasia type 1 (MEN-1) is an autosomal dominant disease involving tumors of the parathyroid, pancreas, and pituitary glands. Over 50% of the patients with this syndrome will have involvement of the pituitary gland. Computed tomography (CT) of the head was performed in 21 of 42 patients with the clinical diagnosis of MEN-1. CT demonstrated pituitary abnormalities in 15 patients, 13 of whom had pituitary endocrine dysfunction. The most common endocrinopathy was hyperprolactinemia, documented in nine patients. Hypopituitarism due to nonfunctional adenoma was found in two patients, and acromegaly and Cushing disease in individual cases. The appearance of the pituitary gland in CT evaluation of the sella in patients with MEN-1 is presented.**

Multiple endocrine neoplasia type 1 (MEN-1), also known as Wermer syndrome [1], is a hereditary disease characterized by tumors of the parathyroid, pancreatic islets, and pituitary gland, in descending order of frequency. Carcinoid tumors, thymomas, thyroid adenomas, and lipomas have also been associated with MEN-1 [2]. The MEN-1 syndrome is inherited in an autosomal dominant fashion [1] with a high degree of penetrance and variable expressivity. Isolated cases of the syndrome occur in up to 50% of reported patients [3].

The parathyroid glands are involved in over 90% of the cases of MEN-1. The findings include hyperplasia or adenoma, usually involving multiple glands. The resulting hypercalcemia may be clinically asymptomatic, especially in younger individuals. Pancreatic islet cell tumors occur slightly less often and may secrete a variety of polypeptide hormones including insulin, glucagon, and gastrin, the latter resulting in the Zollinger-Ellison syndrome.

Over 50% of patients with this syndrome will be found to have pituitary tumors, with pituitary involvement often silent. Before the development of sensitive radioimmunoassays for pituitary hormones, refined techniques for pituitary surgery, and more definitive pituitary cellular typing, the pituitary tumors in MEN-1 were considered to be nonfunctional chromophobe adenomas, except for occasional reports of acromegaly or Cushing disease. Prolactin-secreting tumors have been reported in this syndrome with increasing frequency.

## Materials and Methods

Forty-two patients with the clinical diagnosis of MEN-1 were studied at the National Institutes of Health. In 21 of these, computed

tomographic (CT) head scans were obtained. In 17 patients, scans were obtained on the basis of clinical and/or radiologic suspicion of pituitary pathology. Four patients with a diagnosis of MEN-1 but without evidence of pituitary disease were also included in the study in an effort to detect clinically asymptomatic pituitary tumors.

CT was performed with either an EMI CT 1010 or a GE CT 8800 scanner. On the EMI scanner, scans were obtained at 10 mm slice thicknesses both before and after an intravenous contrast medium bolus injection of 100 ml Hypaque 60. GE scans were obtained usually after similar intravenous contrast injection with direct coronal scans through the sella at 1.5 mm slice thickness and spacing. Five mm slice thickness scans through the sella were also obtained in the axial projection. In one patient, 1.5 mm axial scans were obtained through the sella, followed by reformatting in sagittal and coronal planes. Four patients were examined on the EMI scanner only, 15 on the GE scanner only, and three on both instruments. Plain film examination of the sella was also obtained on all patients. Hormonal assays included basal morning serum prolactin levels. The normal assay range for men is 2–27 ng/ml and for women 2–37 ng/ml. The diagnosis of MEN-1 was made if the patient had at least two of three glands involved (i.e., parathyroid, pancreas, or pituitary) or one gland and a positive family history of the disease.

CT scans were considered abnormal if one or more of the following criteria were present: height of the gland greater than 7 mm as measured on direct coronal scans; an upward convexity of the gland unassociated with the insertion of the infundibulum; focal areas of abnormal attenuation manifest as decreased or increased density relative to the contrast-enhanced pituitary gland; and focal thinning of the floor of the sella at the site of the bulging gland.

## Results

Of the 21 MEN-1 patients having CT head scans, 15 were interpreted as positive and six as negative. Five of the 15 positive scans revealed an enlarged sella with bony erosion and contrast enhancement of an intrasellar mass with suprasellar or parasellar extension (fig. 1). In 10 patients with abnormal CT scans the findings were suggestive of a pituitary microadenoma. Six of these patients had reproducible focal areas of low attenuation greater than 2 mm within a normal or slightly enlarged pituitary (fig. 2). Four patients with abnormal configuration of pituitary had lesions enhancing to a degree equal to or slightly greater than the visualized gland (fig. 3).

Anteroposterior and lateral plain film examination of the sella was considered abnormal in 10 of the 15 patients with CT abnormalities. Sellar changes ranged from thinning and erosion of the lamina dura

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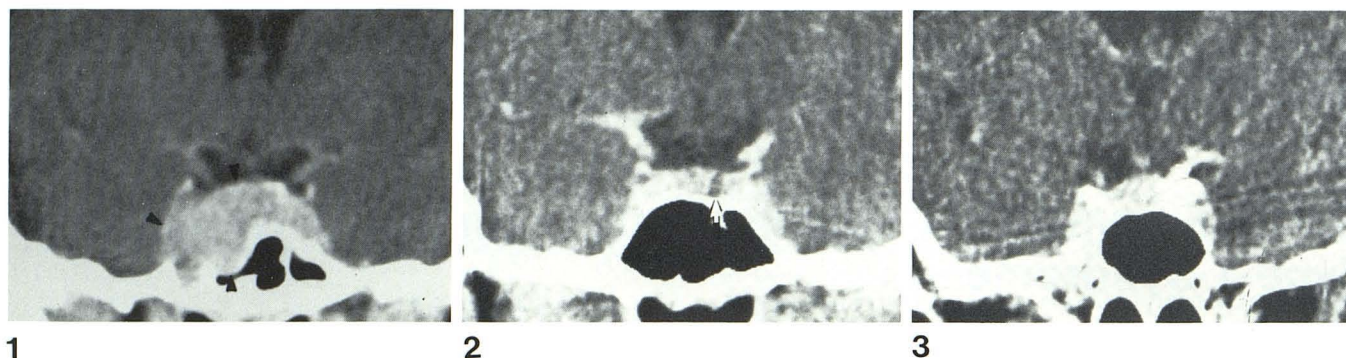


Fig. 1.—Coronal CT scan reveals pituitary macroadenoma with homogeneous contrast enhancement. Adenoma extends into parasellar region on left and erodes floor of sella (arrowheads).

Fig. 2.—Direct coronal contrast-enhanced scan demonstrates convexity of upper border and zone of low density (arrow) in pituitary gland in patient

with hyperprolactinemia.

Fig. 3.—Central zone of increased attenuation below infundibulum in enlarged contrast-enhanced pituitary in patient with MEN-1 and normal pituitary hormonal assays.

TABLE 1: Manifestation of Pituitary Abnormalities in MEN-1 Syndrome

Hormonal Abnormality	No. Cases				
	Totals	Sella		CT	
		+	—	+	—
Hyperprolactinemia (36–576 ng/ml) . . . . .	9	6	3	9	0
Hyperpituitarism . . . . .	2	2	0	2	0
Acromegaly . . . . .	1	1	0	1	0
Cushing disease . . . . .	1	0	1	1	0
Normal . . . . .	8	1	7	2	6
Totals . . . . .	21	10	11	15	6

Note.—+ = positive; — = negative.

to gross destruction of the sella in the larger adenomas. In six patients with suspected microadenomas on sellar CT, plain films appeared normal.

In this series, hyperprolactinemia was the most common hormonal manifestation of pituitary disease, occurring in 10 of our MEN-1 patients (table 1). Seven of 15 patients (six women and one man) with abnormal CT scans had elevated serum prolactin. Three patients had serum prolactin greater than 100 ng/ml, and two had levels greater than 300 ng/ml. Two patients with normal serum prolactin had previously documented hyperprolactinemia; one is receiving bromocriptine therapy. Six patients had normal serum prolactin, including two patients with nonfunctioning pituitary adenomas and one patient with Cushing disease.

CT demonstrated focal areas of hypodensity within a normal-size pituitary and in the presence of normal hormonal assays in two of the four "control" patients in whom there was no clinical evidence of pituitary disease.

Six of our patients had surgically proven pituitary tumors. Two tumors were classified as eosinophilic adenomas, including one acromegalic patient. Two patients had prolactinomas and two had nonfunctional tumors classified as chromophobe adenomas.

## Discussion

The incidence of pituitary adenoma in MEN-1 syndrome in reported series has ranged from 50% to 100% [2–4]. As many as 25% are clinically silent [5], being found on hormonal testing or at autopsy. When symptomatic, the pituitary tumors in this syndrome

usually become clinically apparent between the third and fifth decades. Although the least common element of the classic triad of MEN-1, pituitary tumors may be responsible for the first clinical manifestations of the polyglandular neoplasia [6, 7]. In a previously reported series [3], 15% of MEN-1 patients presented in this manner. Six of our 15 patients with proven or suspected pituitary disease presented in this manner. The pattern of involvement of pituitary disease reveals that it most often occurs in association with hyperparathyroidism and less often in conjunction with both parathyroid and pancreatic disease (table 2).

Recent reports of "nonsecreting" pituitary tumors reveal that as many as 75% secrete prolactin [8–10]. It is not surprising, therefore, that hyperprolactinemia and prolactinomas are being described in MEN-1 with increasing frequency [5, 6, 11–16]. Thirteen of our 15 patients with CT evidence of pituitary abnormality had biochemical evidence of pituitary endocrine dysfunction. Nine of these patients had hyperprolactinemia. Prolactin-secreting tumor was surgically proven in four patients and is suggested in the remaining six, all of whom had abnormal pituitary by CT. Two patients had panhypopituitarism secondary to nonfunctioning adenomas. One patient had pituitary-dependent Cushing syndrome. CT was considered abnormal in all patients with hormonal abnormalities and in two of eight patients with normal hormonal levels. In these two patients, CT demonstrated focal areas of low density within a normal-size contrast-enhanced pituitary gland. It should be emphasized, particularly in light of the recent studies [17], that the criterion of a low-density region in the pituitary is not diagnostic of pituitary adenoma. This finding is also compatible with other pituitary abnor-



TABLE 2: Patterns of Gland Involvement in MEN-1

Pattern	No. Cases (%)
Parathyroid, pancreas, pituitary	6 (14.2)
Parathyroid, pancreas	12 (28.6)
Parathyroid, pituitary	11 (26.2)
Pituitary, pancreas	1 (2.4)
Parathyroid and family history	11 (26.2)
Pancreas and family history	1 (2.4)
Totals	42 (100.0)

malities, including pars intermedia cyst, infarct, abscess, or metastasis. Careful clinical correlation is, therefore, essential in diagnosing pituitary pathology.

Amenorrhea and galactorrhea were the most common presenting symptoms in eight women with hyperprolactinemia. Two had normalized their prolactin levels on bromocriptine therapy. The only man with hyperprolactinemia in only one of 12 family members screened. Thirteen of our patients had a positive family history for MEN-1 syndrome, including five patients with familial incidence of pituitary adenomas. Determination of the true frequency of prolactinomas and the hereditary implications will require a study of a large group of patients over a prolonged period.

The familial association of prolactin-secreting and other pituitary tumors in MEN-1 has yet to be clarified [16, 18, 19]. Farid [16] found prolactin-secreting pituitary adenomas inherited in a dominant fashion in four of 10 family members and also found three other relatives in whom these tumors were present. Marx [18] detected hyperprolactinemia in only one of 12 family members screened. Thirteen of our patients had a positive family history for MEN-1 syndrome, including five patients with familial incidence of pituitary adenomas. Determination of the true frequency of prolactinomas and the hereditary implications will require a study of a large group of patients over a prolonged period.

In conclusion, pituitary tumors, in particular prolactin-secreting tumors, may be the first manifestation of MEN-1 syndrome with concurrent or subsequent evolution of other adenomas. The occurrence of pituitary tumors may conform to an autosomal dominant pattern of inheritance, but may occur idiopathically. The pituitary adenomas in this syndrome appear indistinguishable from isolated pituitary tumors.

On the basis of our findings, a reasonable approach to this clinical problem should include serum calcium determination and careful family history in all patients with prolactin secreting tumors. In addition, serum prolactin determination is recommended in all patients with MEN-1 syndrome as well as their families. High-resolution CT scans of the sella are suggested in all MEN-1 patients with abnormal pituitary hormonal assays or clinical symptoms of pituitary disease.

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