Meningiomas May Be a Component Tumor of Multiple Endocrine Neoplasia Type 1

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Abstract

Purpose: Recently, an increased incidence of some nonendocrine tumors are reported in patients with multiple endocrine neoplasia type 1 (MEN 1). There are rare reports of meningiomas and other central nervous system tumors in these patients, but it is unknown if they are more frequent or if allelic loss of the MEN1 gene is important in their pathogenesis. The aim of this study was to address these two latter questions.

Experimental Design: Results from a prospective study of 74 MEN 1 patients with suspected/proven pancreatic endocrine tumors (PETs) were analyzed, as well as molecular studies performed on a resected meningioma. All patients had serial brain imaging studies (computed tomography, magnetic resonance imaging, and octreoscopy since 1994) and yearly studies evaluating MEN 1 involvement with a mean follow-up of 7.2 years. Results were compared with 185 patients with sporadic Zollinger-Ellison syndrome.

Results: Six patients (8%) had meningiomas. Meningiomas were single and found late in the MEN 1 course (mean age = 51 years). Magnetic resonance imaging/computed tomography were more sensitive than octreoscopy. Their diagnosis averaged 18 years after the onset of hyperparathyroidism, 10–15 years after pituitary disease or PETs. Meningiomas were 11 times more frequent in patients with PETs with MEN 1 than without MEN 1 (P = 0.017). No clinical, laboratory, or MEN 1 feature distinguished patients with meningiomas. Meningiomas were asymptomatic and 60% showed no growth. A resected meningioma showed loss of heterozygosity at 11q13 and 1p, including at p73 and ARHI/NOEY2 locus, but not at the neurofibromatosis 2 gene locus.

Conclusions: These results show meningiomas are not an infrequent occurrence in MEN 1, and loss of the function of the MEN1 gene product plays a role in their pathogenesis in these patients.

Introduction

Multiple endocrine neoplasia type 1 (MEN 1) is an autosomal dominant disorder caused by mutations in the MEN1 gene on chromosome 11q13 (1, 2). Patients characteristically develop tumors of the parathyroid, enteropancreatic tissue, and anterior pituitary (1–4). More recently, an increased occurrence of other endocrine tumors as well as nonendocrine tumors are reported in patients with MEN 1, including skin tumors (melanomas, collagenomas, and angiofibromas), carcinoids (thymus, lung, and gastric), lipomas, as well as tumors of the adrenal and smooth muscle (1, 2, 5–15). Some of these tumors [parathyroid, pituitary, pancreatic endocrine tumors (PETs), carcinoids, smooth muscle, and skin tumors] have allelic losses at the MEN1 locus on 11q13; therefore, alterations in the MEN1 gene play a key role in their pathogenesis, whereas with others (thymic carcinoids, and adrenal), this is not the case (1, 2, 5–15) and their pathogenesis remains unclear.

Central nervous system (CNS) tumors, including ependymomas (16, 17), schwannomas (9, 18, 19), and meningiomas (20, 21), have rarely been reported in patients with MEN 1 or MEN 1-variant syndromes. However, some of the tumors such as meningiomas are common CNS tumors in the general population with an annual rate of 7.8/100,000, comprising 20% of all CNS tumors (22) and have rarely been reported in MEN 1 (20, 21). Therefore, whether meningiomas or any of these CNS tumors occur with increased frequency in patients with MEN 1 is unknown. It is also unknown if they do occur whether allelic losses in the MEN1 gene are found in these tumors, and therefore, alterations in this gene plays a central role in their pathogenesis in MEN 1 patients.

In our ongoing prospective study of patients with possible PETs with MEN 1, in addition to serial evaluations of MEN 1 involvement, CNS assessments using brain magnetic resonance imaging (MRI) and computed tomography (CT) are performed initially and at yearly evaluations. This study reports the analysis of this prospective study and reveals that 8% of the 74 patients with MEN 1 followed up to 19 years developed meningiomas. A comparison with similar patients without MEN 1 with PETs showed this was a highly significant increase and molecular studies of a meningioma from a MEN 1 patient revealed allelic loss at 11q13 at the MEN1 locus as well as at chromosome 1p but not at the neurofibromatosis 2 (NF2) locus.
Materials and Methods

One hundred twenty-eight consecutive patients with MEN 1 with or without Zollinger-Ellison syndrome (ZES) evaluated between July 1975 and August 2002 at NIH were considered for this study. Patients were eligible for the study if they had regular pituitary and whole brain imaging with CT scanning or MRI. This study is part of an ongoing prospective study of patients with ZES with or without MEN 1 since 1975 and is approved by the Clinical Research Committee of the National Institute of Diabetes, Digestive, and Kidney Diseases.

Diagnostic criteria for MEN 1, as previously described (23, 24), included presence of a combination of PET, pituitary disease, hyperparathyroidism, positive genetic test for MEN 1, or the presence of any of the above with a known family history of MEN 1. Of the 74 patients with MEN1, we have completed sequencing of the MEN1 gene in 62 patients, of which, 90% had a germ-line mutation. We have not sequenced all of the patients with sporadic ZES; however, we have sequenced 35 consecutive cases of sporadic ZES, including 1 patient with sporadic ZES with a meningioma and none had MEN1 gene mutations. The presence or absence of a PET was determined by surgical exploration or by imaging alone. The diagnosis of ZES was made biochemically as described previously (25). Serum gastrin concentrations were measured by Bioscience Laboratories (New York, NY) and by Mayo Clinic Laboratories (Rochester, MN).

Study Protocol. During the initial evaluation at the NIH, all patients underwent studies to determine the extent of involvement of MEN 1 as described previously (23, 24). These included a detailed review of symptoms compatible with gastric acid hypersecretion, a personal or family history of MEN 1-related symptoms, and laboratory studies to assess for presence of hormonal activity (parathyroid, pituitary, adrenal, and pancreas). Laboratory studies included measurement of serum parathyroid hormone (intact and mid-molecule), prolactin, fasting serum gastrin, calcium (ionized and total), proinsulin, insulin and simultaneous glucose, growth hormone, glucagon, adrenocorticotropic hormone, thyrotropin, chromogranin A, pancreatic polypeptide, albumin, and urinary cortisol. For the diagnosis of ZES, the patients had assessment of gastric acid secretory rate, measurement of fasting serum gastrin concentration on 3 separate days (25), and secretin provocative testing (when secretin was available) with a bolus injection of 2 clinical units of secretin/kg body weight (25, 26). To define the extent and location of PETs, all patients underwent abdominal imaging as previously described (27, 28) with ultrasound, CT scanning with i.v. contrast, MRI, and selective abdominal angiography if the results were unclear. Somatostatin receptor scintigraphy (SRS) was performed routinely since 1994 by injection of $^{111}$In-DTPA-d-Phe$^1$ octreotide followed by whole body as well as single-photon emission computed tomography images as described previously (27, 28). The onset of a PET was determined either as the time of onset of symptoms in the patients with functional PETs or as the time of the first imaging diagnosis with a nonfunctional PET. The duration of the PET was determined as the time of onset of the PET until their last follow-up or death.

The onset of MEN 1 was determined as the time of onset of symptoms compatible with MEN 1, including nephrolithiasis, pituitary disease, symptomatic PET, detection of a PET, or the time of first detection of an abnormal laboratory value compatible with MEN 1 hormonal overactivity in an asymptomatic patient with known family history of MEN 1. The time of diagnosis of MEN 1 was the time of confirmation of MEN 1 at the initial visit or the time of first diagnosis before NIH presentation at an outside institution. In patients with multiple parathyroidectomies, the initial parathyroid surgery was taken for measurement of years from parathyroidectomy.

All patients had brain imaging with a CT scan or MRI as well as imaging of the pituitary fossa initially and during each subsequent evaluation. MRI was generally used with CT scanning performed in patients with a contraindication to MRI. In patients with any abnormality, both studies were done. MRI scans were performed using a 1.5-T magnet (General Electric, Milwaukee, WI). T1-weighted (repetition time in ms/echo time in ms, 415-550/11-16) and T2-weighted (2500-4384/90-110) spin-echo images were obtained, with a 5-mm section of thickness. The T1-weighted scans were repeated after the administration of 0.1 mmol of gadopentetate dimeglumine/kg body weight (Magnevist; Berlex Laboratories, Wayne, NJ). CT scans were performed using Isovue (Bracco Diagnostic, Inc., Princeton, NJ). The time of diagnosis of a meningioma was determined as the first time it was identified on imaging. An experienced neuroradiologist (N. P.) diagnosed all meningiomas. The radiological diagnosis of meningioma was made by the presence of an extra axial dural-based mass that was uniformly and markedly enhanced with contrast materials (22, 29, 30). Possible symptoms of the meningioma were evaluated by a detailed review of likely CNS symptoms. The largest diameter of each meningioma was determined initially and compared with the diameter in the last study to assess change in size of the meningioma.

All patients had serial studies with all but 1 patient in the present study having serial follow-up evaluations at least yearly. During the follow-up visits, in addition to brain and pituitary imaging, abdomen imaging, as well as the plasma hormone assays listed above that were performed on the initial study, were all repeated. Patients with metastatic disease had follow-up visits every 3–6 months to assess changes in extent of the metastases as described previously (31, 32).

The frequency of meningiomas in the 65 patients with MEN 1 with ZES was compared with that of 185 patients with ZES without MEN 1 (i.e., sporadic ZES) who had undergone similar brain imaging studies.

Statistics. Continuous variables were compared using the Mann-Whitney U test and discontinuous variables using Fisher’s exact test or $\chi^2$ test. $P < 0.05$ was considered significant. Results are reported as mean ± SE.

DNA Samples. Tumor tissue from the meningioma of 1 of the patients with MEN 1 was obtained by microdissection from the formalin-fixed, paraffin-embedded sample. Tumor tissue was microdissected from four different areas on one slide and was digested in four tubes to release tumor genomic DNA by a 3-day incubation in 30 μl of TE solution [10 mm Tris (pH 8.0)-1 mM EDTA, 0.5 mg/ml proteinase K, 0.5% Tween 20] at 37°C. Normal genomic DNA from the patient as well as from her mother was isolated from peripheral blood leukocytes using...
Table 1  Comparison of clinical and laboratory characteristics of patients with multiple endocrine neoplasia type 1 (MEN 1) with and without meningiomas

<table>
<thead>
<tr>
<th>Number (percentage)*</th>
<th>Meningioma present</th>
<th>Meningioma absent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient number</td>
<td>6</td>
<td>68</td>
<td>74</td>
</tr>
<tr>
<td>Age at onset of MEN 1 (yrs)b</td>
<td>33.2 ± 5.9</td>
<td>29.8 ± 1.2</td>
<td>30.1 ± 1.2</td>
</tr>
<tr>
<td>Age at diagnosis of MEN 1 (yrs)</td>
<td>41.8 ± 9.2</td>
<td>36.0 ± 1.4</td>
<td>36.5 ± 1.5</td>
</tr>
<tr>
<td>Age at diagnosis of hyperparathyroidism (yrs)</td>
<td>40.0 ± 9.9</td>
<td>35.4 ± 1.3</td>
<td>35.7 ± 1.3</td>
</tr>
<tr>
<td>Male gender</td>
<td>2 (33%)</td>
<td>32 (47%)</td>
<td>34 (46%)</td>
</tr>
<tr>
<td>Follow-up duration at NIH (yrs)c</td>
<td>7.6 ± 4.2</td>
<td>7.2 ± 0.8</td>
<td>7.2 ± 0.8</td>
</tr>
<tr>
<td>MEN 1 duration (yrs)d</td>
<td>20.5 ± 6.2</td>
<td>18.4 ± 1.4</td>
<td>18.6 ± 1.4</td>
</tr>
<tr>
<td>MEN 1-related death during follow-up</td>
<td>0 (0%)</td>
<td>2 (3%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Family history of MEN 1</td>
<td>5 (83%)</td>
<td>50 (73%)</td>
<td>55 (74%)</td>
</tr>
<tr>
<td>Fasting serum gastrin (pg/ml)*</td>
<td>425 ± 297</td>
<td>23,500 ± 14,000</td>
<td>21,675 ± 12,800</td>
</tr>
<tr>
<td>Median</td>
<td>165</td>
<td>735</td>
<td>577</td>
</tr>
<tr>
<td>(Range)</td>
<td>(28–1,900)</td>
<td>(24–930,000)</td>
<td>(24–930,000)</td>
</tr>
<tr>
<td>Serum chromogranin A (ng/ml)*</td>
<td>227 ± 110</td>
<td>470 ± 149</td>
<td>448 ± 136</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>(12–582)</td>
<td>(4.3–6,639)</td>
<td>(4.3–6,639)</td>
</tr>
<tr>
<td>(Range)</td>
<td>27.5 ± 8.4</td>
<td>26.9 ± 5.9</td>
<td>26.9 ± 5.5</td>
</tr>
<tr>
<td>Serum prolactin (µg/liter)*</td>
<td>227 ± 110</td>
<td>470 ± 149</td>
<td>448 ± 136</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>(12–582)</td>
<td>(4.3–6,639)</td>
<td>(4.3–6,639)</td>
</tr>
<tr>
<td>(Range)</td>
<td>27.5 ± 8.4</td>
<td>26.9 ± 5.9</td>
<td>26.9 ± 5.5</td>
</tr>
</tbody>
</table>

* Percentage of MEN 1 patients with the characteristic in the indicated meningioma category.

b Age at first MEN 1 symptom or discovery of abnormal laboratory value.

c Time from first NIH evaluation to present.

d Time from MEN 1 onset to present.

The Puregene DNA isolation kit (Gentra System, Minneapolis, MN). DNA was stored at 4°C until PCR amplification.

**Microsatellite DNA Markers.** Six polymorphic markers (D11S480, D1S1883, PYGM, D11S4946, D11S449, and INT-2) spanning the MEN1 locus (33, 34) and 5 markers spanning the NF2 suppressor gene (D22S268, D22S1163, D22S929, D22S280, and D22S282; Ref. 35) as well as 12 markers spanning chromosome 1p were ordered from Invitrogen, ResGen

Table 2  Comparison of MEN 1 features in patients with or without meningioma

<table>
<thead>
<tr>
<th>Number (percentage)*</th>
<th>Meningioma present (n = 6)</th>
<th>Meningioma absent (n = 68)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperparathyroidism present</td>
<td>5 (83%)</td>
<td>68 (100%)</td>
<td>73 (98%)</td>
</tr>
<tr>
<td>Years from parathyroidectomyb</td>
<td>15.8 ± 7.0</td>
<td>12.5 ± 1.4</td>
<td>12.7 ± 1.3</td>
</tr>
<tr>
<td>Pancreatic endocrine tumor (PET) present</td>
<td>4 (67%)</td>
<td>61 (90%)</td>
<td>65 (96%)</td>
</tr>
<tr>
<td>Zollinger-Ellison syndrome</td>
<td>4 (67%)</td>
<td>61 (90%)</td>
<td>65 (96%)</td>
</tr>
<tr>
<td>Duration of PETc</td>
<td>11.2 ± 5.8</td>
<td>11.0 ± 1.0</td>
<td>11.0 ± 1.0</td>
</tr>
<tr>
<td>PET extentd</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver metastasis</td>
<td>4 (67%)</td>
<td>47 (69%)</td>
<td>51 (69%)</td>
</tr>
<tr>
<td>PIT Resection</td>
<td>3 (50%)</td>
<td>39 (57%)</td>
<td>42 (57%)</td>
</tr>
<tr>
<td>Year from PET resectionb</td>
<td>5.6 ± 3.9</td>
<td>7.4 ± 1.0</td>
<td>7.3 ± 0.9</td>
</tr>
<tr>
<td>Pituitary adenoma present</td>
<td>3 (50%)</td>
<td>27 (40%)</td>
<td>30 (40%)</td>
</tr>
<tr>
<td>Pituitary adenoma resection</td>
<td>1 (17%)</td>
<td>9 (13%)</td>
<td>10 (14%)</td>
</tr>
<tr>
<td>Years from adenoma resectionb</td>
<td>37.8</td>
<td>10.3 ± 2.6</td>
<td>13.0 ± 3.6</td>
</tr>
<tr>
<td>Other tumorsc</td>
<td>1 (17%)</td>
<td>16 (24%)</td>
<td>17 (23%)</td>
</tr>
</tbody>
</table>

* Percentage in each meningioma category.

b Years from surgery to present.

c Years from diagnosis of PET to present.

d Extent determined by surgical pathology (n = 42) or radiological imaging (n = 32). ‘Localized’ refers to presence of a PET without distant metastasis (i.e., bone, liver).

Other tumors include: papillary thyroid cancer (n = 1); prostate cancer (n = 1); renal cell papillary cancer (n = 1); basal cell cancer (n = 2); uterine fibroid (n = 1); renal cystadenoma (n = 1); renal angiolioma (n = 1); esophageal leiomyosarcoma (n = 2); esophageal cancer (n = 1); melanoma (n = 3); uterine leiomyosarcoma (n = 1); bladder cancer (n = 1); uterine adenocarcinoma (n = 1); rhabdomyosarcoma sarcoma (n = 1); and colon cancer (n = 1).
Meningiomas in MEN 1

Onset of pituitary disease to meningioma
Mean ± SE 14.1 ± 11.4
(Range) (0.5–37)

Years from pancreatic endocrine tumor resection to meningioma
Mean ± SE 4.0 ± 4.1
(Range) (0.4–12)

Parathyroidectomy
Mean ± SE 4.1 ± 11.5
(Range) (2.6–27.7)

% increase in size (mm)
Mean ± SE 7.6 ± 0.7
(Range) (5.5–12.7)

Results

Seventy-four patients met the study criteria in that they all had brain and pituitary imaging on admission and subsequent follow-ups. In these 74 patients, 92% had an initial MRI, and the remainder had an initial CT either because MRI was not available at the time or was contraindicated. The 74 patients had a mean age of onset and diagnosis of MEN 1 in the fourth decade, and mean duration of total follow-up from MEN 1 onset was 19 years with 7.2 years occurring at NIH (Table 1).

A meningioma was identified in 6 of the 74 patients by imaging (Table 1). In the 6 patients with meningiomas, 5 of 6 (83%) had hyperparathyroidism, 4 of 6 (67%) had a PET with ZES, and 3 of 6 (50%) had a pituitary adenoma (Table 2). Meningioma was found late in the course of the MEN 1 with a mean time of 17.6 years after the onset of the MEN 1 (Table 3) at a mean age of 51 years. However, there was a wide range in age at diagnosis of the meningioma, varying from 29 to 76 years (Table 3). The meningioma was diagnosed on the average 18 years after the onset of hyperparathyroidism and 14 years after the onset of ZES and pituitary disease (Table 3). Meningiomas were also diagnosed after patients had been treated for the more common manifestations of MEN 1 with parathyroidectomies, pituitary surgery, or resection of a PET (Table 3). In no case was the meningioma diagnosed caused by symptoms, instead in all 6 cases, it was found on routine imaging studies (Table 4).

MEN 1 patients with or without meningiomas did not differ in their age at onset or at diagnosis of MEN 1, age at diagnosis of hyperparathyroidism, percentage with male gender, duration of follow-up for MEN 1-related disorders, percentage with a family history of MEN 1, the mean serum prolactin, or the mean chromogranin A levels (Table 1). The mean serum gastrin level (Carlsbad, CA) based on the published papers (36) and online data.

PCR. The tumor DNA and leucocyte DNA of the patient, as well as the leucocyte DNA of her mother, were amplified by PCR using a GeneAmp PCR system 9700 Thermocycler (PE Applied Biosystems, Foster City, CA) with the following conditions: 94°C for 5 min; 94°C for 45 s; annealing at 59°C for 45 s; and extension at 72°C for 45 s for total 35 cycles. Each reaction contained 1.5 μl of PCR buffer, 1.5 μl of tumor DNA or normal control DNA (~10–20 ng), 10 pmol of each primer, 2.5 units of Gold Taq polymerase (PE Applied Biosystems), and 130 μM each of deoxynucleoside triphosphate. The final concentration of Mg²⁺ was 1.5 mM, and α-P₃²-dCTP (0.1 μl/reaction; >3000 Ci/mmol) was included in each PCR reaction.

Analysis of Allele Loss. After PCR, products were mixed with loading dye (v/v = 1/1), denatured at 95°C for 10 min, then chilled immediately at 4°C. Four μl of products were analyzed by electrophoreses through a 6 or 8% denaturing polyacrylamide gel in 1× Tris-borate EDTA buffer. The gels were then dried and exposed to X-ray films (Eastman Kodak Company, Rochester, NY) with or without an intensive screen for 8 h to 3 days. The intensity of signals in the films was analyzed and quantified by using Kodak Image station 440 system (Eastman Kodak Company). Loss of heterozygosity (LOH) was defined as a reduction of at least 50% observed in the allelic ratio between the tumor and normal DNA (37, 38).

Five of the six patients had octreotide scan.

Five of the six patients had follow-up imaging. One patient had meningioma recently discovered.
was significantly higher in patients without meningiomas \( (P < 0.02 \) without correction for multiple, highly correlated comparisons; Table 1).

The manifestations of MEN 1 in patients with or without a meningioma are compared in Table 2. Almost all patients in the nonmeningioma (83%) and meningioma (100%) groups had hyperparathyroidism, and the percentage having a previous parathyroidectomy at the time the meningioma was diagnosed was not significantly different (85 versus 67%, \( P = 0.24 \) nor was the duration from the parathyroidectomy (Table 2). The majority of the patients in the meningioma group (67%) had a PET with ZES, as did the patients in the nonmeningioma group (90%), and the duration of the PET was not significantly different in the two groups (i.e., 11.2 and 11.0 years; Table 2). The extent of the PET was similar in both groups with each having two-thirds of the patients with localized disease (Table 2). Although there was a trend for patients without a meningioma to have more aggressive PETs with liver metastases (20 versus 0%), this difference did not reach significance. Patients with or without meningioma did not differ in the percentage who had previous PET resections (~50%) or the time from these resections (Table 2). Pituitary adenomas occurred in 40% of all the patients and neither their frequency, percentage of the patients requiring pituitary surgery, nor the duration of time from that surgery differed between the two groups (Table 2). Other non-MEN 1-related cancers (prostate, renal, uterine, esophageal, bladder, and colon) and less common MEN 1-related tumors (thyroid cancer, angiolipoma, leiomyomata, melanoma, leiomyosarcoma; Refs. 4–7) occurred in 23% of the patients, and their frequency did not differ in patients with or without meningiomas (Table 2).

Two of the 6 meningiomas were in the frontal lobe, 3 in the planum sphenoidale, and 1 in the posterior fossa (Table 4). Five of the 6 patients had an octreotide scan performed that included whole body images, and in 3 patients, there was uptake in the brain area corresponding to the site of meningioma on the MRI. Examples of the somatostatin receptor scintigraphy and MRI results in 2 patients are shown in Figs. 1 and 2. In the patient shown in Fig. 1, the meningioma in the dura of the planum sphenoidale was seen on both the MRI and somatostatin receptor scintigraphy studies, whereas in the patient in Fig. 2, the meningioma seen in the left frontal lobe with the MRI was not seen on the somatostatin receptor scintigraphy study. The mean initial size of the meningiomas was 16 mm with a range of 8–30 mm (Table 4). The average follow-up duration of the meningioma was 3.6 years with a range of 0.5–11 years. One patient with a 30-mm meningioma underwent resection. Two of the 5 meningiomas evaluated for changes in size over time showed an increase in size with an average increase of 1.4 mm or 16.7% of their original length, which represented a 17.3% increase in their original length/year of follow-up (Table 4). The patient with the greater increase in size of the meningioma was a patient with

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**Fig. 1** Magnetic resonance imaging (MRI) and somatostatin receptor scintigraphy (SRS) showing location of the meningioma in a patient (no. 5) with multiple endocrine neoplasia type 1. **Left panel**, coronal (top) and sagittal (bottom) after contrast views of the T1-weighted MRI images. An extracerebral mass is identified originating form the dura of the planum sphenoidale. The mass compresses the inferior aspect of the left frontal lobe and projects into the interhemispheric fissure. There is homogeneous enhancement present. These findings are typical for meningioma. **Right panel**, coronal (top) and transverse (bottom) views on SRS showing enhanced uptake of radionucleotide in the meningioma.
two prior pituitary surgeries and postoperative radiation. He has also had other MEN 1-related conditions, including hyperparathyroidism, ZES, and had an early age of presentation of the MEN 1. None of the other patients with meningiomas had received radiation.

To compare the frequency of meningioma in patients with ZES with or without MEN 1, the rate of occurrence of meningiomas of 4 cases in 65 patients with ZES and MEN 1 was compared with that in 185 patients with ZES without MEN 1 who also had repeated brain imaging. Each of the 185 patients with sporadic ZES (i.e., without MEN 1) were involved in a prospective protocol with yearly evaluations with biochemical and imaging studies similar to that outlined for the MEN 1 patients in “Materials and Methods.”

Meningiomas were significantly ($P = 0.017$) more frequent in the patients with ZES and MEN 1 [6.2% (4 of 65) versus 0.5% (1 of 185), respectively]. This difference occurred although the 185 patients without MEN 1 were older (49.8 ± 0.8 versus 47.7 ± 1.8 years, $P < 0.058$) and had a longer follow-up at the NIH (10.3 ± 0.4 versus 8.0 ± 0.9 years, $P = 0.0011$). Furthermore, this difference in frequency was not due to the difference in duration of the ZES (17.7 ± 0.6 versus 17.1 ± 1.2 years, $P = 0.49$), male gender (46 versus 57%, $P = 0.09$), or the severity of the ZES because fasting gastrin levels (median, 610 versus 1000 pg/ml, $P = 0.10$) were not significantly different, and in fact, the basal acid output was higher in the sporadic cases (44.9 versus 41.6 mEq/h, $P = 0.044$).

Previous studies have shown a high frequency of LOH on chromosome 1p LOH (28–57%) and at 22q12 (44–100%) at the NF2 tumor suppressor gene locus (28, 35, 39–48) in sporadic meningiomas and in NF2-associated meningiomas (49), and their presence correlates with an aggressive growth pattern, tumor site, high histological grade, and decreased recurrence-free survival (40, 41, 44–46). To assess these genetic alterations (NF2 and 1p) as well as possible LOH at the MEN1 locus on chromosome 11q13 in this MEN 1-associated meningioma, each of these regions was examined with polymorphic microsatellite markers (Figs. 3–5). On chromosome 11q13, LOH was identified by all six polymorphic markers over the MEN1 locus (Figs. 3 and 5). No LOH was found on chromosome 22q in the region of the NF2 gene (Figs. 3 and 5). LOH was identified in six loci of 1p (Figs. 4 and 5). LOH in chromosome 1p at the D1S468 locus indicated loss of p73 gene (50), the homologue of p53 (51, 52). Loss of another novel putative tumor suppressor gene, ARHI/NOEY2, on 1p31 (53), was identified with three markers flanking the gene (D1S2638, D1S1665, and D1S500) and one intragenic marker (D1S2829; Ref. 36; Figs. 4 and 5). ARHI/NOEY2 is a maternal imprinted gene (53), whereas p73 may be a paternal imprinted gene (51). By comparing the allelotyping data of the patient’s normal DNA with her mother’s normal DNA amplified by PCR using marker D1S468, it was demonstrated that the paternal allele of p73 is lost in the tumor (i.e., the upper band disappeared in the tumor; Fig. 4). Similarly, loss of the paternal allele (functional allele) of ARHI/NOEY2 in this meningioma (T1) was shown with markers D1S2638 (data not shown) and D1S1665 that flank ARHI/NOEY2 gene (Ref. 36; Fig. 4). These data demonstrated that ARHI/NOEY2 gene was completely inactivated in the meningioma by loss of its func-
Discussion

LOH at the MEN1 locus on chromosome 11q13 has been identified in many of the endocrine tumors that occur in patients with MEN 1, including PETs, parathyroid tumors, pituitary tumors, cutaneous angiofibromas, smooth muscle leiomyomas, lipomas, and carcinoids of the lung and stomach (2, 3, 5–7, 10–12, 25, 60, 68, 69, 71, 72). Also, the phenotype of MEN 1 knockout mice is similar to the features of the human MEN 1 disorder (55), suggesting that loss of this tumor suppressor gene plays a critical role in the pathogenesis of this disorder. However, in a subset of the tumors mentioned above, MEN1 LOH was not identified (5, 7–10, 54). Moreover, in some tumors that occur in MEN 1 patients such as most adrenocortical tumors, thyroid tumors, and all thymic carcinoids, no LOH of the MEN1 gene is identified (2, 5, 11, 17). These findings suggested that the molecular pathogenesis of these various tumors differ. In the present study, we demonstrated for the first time that a MEN 1-related meningioma had LOH at all six loci examined on the MEN1 gene. This result demonstrates that the meningioma occurring in this patient is an MEN 1 tumor and that alterations in the MEN1 gene play a role in its pathogenesis.

Although this study is the first to establish the occurrence of meningioma as a specific MEN 1 tumor, two previous studies (20, 21) report a meningioma in a patient with MEN 1. Although MEN 1 was not proven, meningiomas have been reported in patients with hyperparathyroidism (56–58) and in patients with pituitary adenomas (57, 60–63). The association of meningiomas with pituitary adenomas is complicated by the recognition that intracranial irradiation for pituitary disease or other causes is associated with occurrence of meningiomas (60, 62, 64, 65). Patients with pituitary adenomas and meningiomas without previous radiation are described previously (60, 61, 63); however, in no case was the presence of MEN 1 investigated. Only 1 of our patients with MEN 1 had previous pituitary radiation, so this suggests pituitary irradiation is not necessary for the development of meningiomas in MEN 1 patients. However, these results do not exclude the possibility that meningiomas could be more frequent in MEN 1 patients receiving pituitary radiation. In addition to the above associations, a patient with a meningioma, gastric myofibroma, thyroid disease, and an ileal carcinoid tumor has been previously reported (66), as well as a patient with multiple lipomas, thyroid disease, prolactin-secreting pituitary adenoma, and meningioma (63).

Other CNS tumors, including spinal ependymomas (16, 17) and schwannomas (19, 20), are occasionally reported in patients with MEN 1 (16, 67) or MEN 1-variant syndromes (19). However, in none of these tumors have studies established that they demonstrate LOH at the MEN1 locus as was shown in the present study for meningiomas in MEN 1 patients. Although the exact factors are unknown that contribute to the development of meningiomas in MEN 1 patients and perhaps these other CNS tumors, a possible contributing factor in some patients could be elevated plasma levels of either gastrin or other gastrointestinal hormones that are frequently secreted by gastrinomas and other PETs these patients commonly develop (25, 68, 69). Gastrin has been shown to cause the proliferation of meningiomas as well as other CNS tumors (70) and meningiomas and other CNS tumors shown to possess CCK/gastrin receptors (71, 72) as well as neurotensin receptors (73), a hormone frequently released by gastrinomas as well as other PETs (68, 74). The present study provides some insights into this possibility. Meningiomas were 11 times more frequent in patients with ZES and MEN 1 than with ZES alone. This difference was not because of the MEN 1 patients being older, having higher serum gastrin levels, more severe ZES, or longer follow-up. These results suggest that the

Fig. 3 Assessment of chromosome 11q13 (left panel) and 22q (right panel) loss of heterozygosity (LOH) in a meningioma from a patient with multiple endocrine neoplasia type 1 (MEN 1). Shown are results from normal tissue (N, i.e., leukocytes) and from tumor (T1). The thin arrows show the retained allele, and bold arrows show LOH. In the left panel are shown results of assessment for 11q13 LOH (MEN1 locus) using marker D11S480, D11S1883, PYGM, and D11S449. MEN1 LOH in the meningioma is seen with all four markers. In the right panel are shown results of assessment for LOH in 22q at the neurofibromatosis 2 (NF2) loci with marker D22S280 and D22S929 (intragenetic marker). No NF2 LOH is seen.

lof heterozygosity, i.e., paternal allele, whereas p73 might not be completely inactivated because it lost the imprinted paternal allele. LOH of NF2 gene, which was shown to be frequently present in sporadic meningiomas (35, 39–41), was not shown in this MEN 1-related meningioma (Figs. 3 and 5).
presence of the MEN 1 is the important contributing factor to the increased frequency of meningiomas in MEN 1 patients. Secondly, there was no correlation in our study with the presence or absence of a meningioma and the magnitude of hypergastrinemia. Thirdly, 2 of the 6 patients with MEN 1 with meningiomas in the present study did not have hypergastrinemia or any PET imaged, demonstrating meningioma can occur without associated ZES or another PET.

The meningiomas in patients with MEN 1 have similarities and differences from those reported in patients without MEN 1. They resemble sporadic meningiomas with a female predominance of 2:1 in MEN 1 patients similar to the 2:1 or 3:2 ratio reported in sporadic meningiomas (22). In all patients with MEN 1, the meningiomas were asymptomatic and detected by imaging studies, whereas 40–80% are symptomatic in patients with sporadic meningiomas in different series (22, 75–77). In comparison to patients with asymptomatic sporadic meningiomas, the mean age of our patients with MEN 1 at the time of diagnosis of the meningioma was lower [51 versus 57–67 year (six studies; Refs. 29, 75, 77–80)]. However, the mean age in our patients at diagnosis of the meningioma was not as low as the third or fourth decade usually seen in patients with NF2 (81). The mean size of the meningioma in our patients at initial detection was smaller than those with asymptomatic sporadic meningiomas [i.e., 1.6 versus 2.2 cm (29), 2.9 cm (75), 2.1 cm (78), or 2.6 cm (82)]. Although the numbers of meningiomas in

Fig. 4 Results of assessment for loss of heterozygosity (LOH) at 1p in a meningioma from a patient with multiple endocrine neoplasia type 1. In the left panel is shown the chromosome location of the loci identified by the different markers. In the middle panel are shown results from normal tissue (N; i.e., leukocytes) and from two different areas of the meningioma (T1 and T2). The thin arrows show the retained allele, and bold arrows show LOH. In the right panel are shown results from the leukocyte DNA of the patient with the meningioma (D) and from her mother (M). The arrows in the right panel show the paternal allele and maternal allele in the patient’s normal tissue. The middle panel shows that the top allele is lost in the meningioma at locus D1S468. Comparison with the D1S468 data in the right upper panel from the patient’s normal tissue (D) and her mother’s normal tissue (M) indicates that there is loss of the paternal allele at D1S468 (i.e., p73) in the meningioma. In the middle panel at locus D1S2638, D1S2829 (intragenetic marker), and D1S1665, the meningioma had LOH of the ARHI/NOEY2 gene. In the T18 meningioma, the top allele and bottom allele are lost at D1S2638 and D1S1665, respectively. Comparison with the data of D1S1665 from the patient and her mother’s normal tissue in the right panel indicates that there is loss of the paternal allele (functional allele) of ARHI/NOEY2 gene in the meningioma (T18). Also the lower allele is lost in the T20 meningioma, which indicates loss of the maternal allele (imprinted allele) of ARHI/NOEY2 gene at this site in the meningioma (T20).
High affinity (i.e., densities of somatostatin receptors which bind octreotide with high affinity (i.e., sst 3, 5)) and that radiolabeled octreotide can be used to image these tumors (83–87). Our data show that meningiomas in patients with MEN 1 also frequently possess high densities of these receptors, with 60% (3 of 5) of patients with meningiomas who underwent somatostatin receptor scintigraphy having a positive scan. This percentage may be lower than the 98–100% reported in studies of sporadic meningiomas (83–87), possibly because of the smaller size of the meningiomas in our patients. Recently, studies imaging PETs with somatostatin receptor scintigraphy demonstrate the detection rate is proportional to tumor size and a similar relationship may exist for meningiomas (88). These results demonstrate that it is not sufficient to rely on somatostatin receptor scintigraphy to detect all patients with MEN 1 with meningiomas but instead an MRI of the brain should be performed at the time of evaluation for possible pituitary adenoma.

A number of different endocrine (parathyroid, pituitary, PETs, and adrenal) and nonendocrine (cutaneous angiofibromas, smooth muscle leiomyomas, thymic and gastric carcinoids, and lipomas) tumors (4, 5, 7, 8, 54) can develop in patients with MEN 1, and the current study provides some insights into the frequency and temporal relationship between some of these tumors and meningiomas in these patients. Meningiomas were found in 8% of the MEN 1 patients studied, which was significantly less frequent than the frequency in the same patients of parathyroid hyperplasia (98%), PETs (96%), or pituitary adenomas (40%). This frequency, however, was similar to that for smooth muscle tumors (4%) in these patients and is approximately equal to that reported for bronchial or thymic carcinoids (0–8%) in MEN 1 patients (2, 14, 15), less frequent than gastric carcinoids (15–35%; Ref. 15), adrenocortical tumors (16–40%; Refs. 2, 12), lipomas (20–34%; Refs. 2, 3), or cutaneous angiofibromas (88%; Ref. 2). The higher frequency of occurrence of meningiomas in females with MEN 1 (2:1) is similar to pituitary adenomas and bronchial carcinoids in MEN 1 patients, which are also more frequent in females (3) but differs from thymic carcinoids that occur almost exclusively in men (14), and hyperparathyroidism or PETs, which occur with equal frequency in MEN 1 patients of both sexes (3). In general, the development of a meningioma was a late feature of MEN 1, occurring 10–15 years later than the development of hyperparathyroidism, PETs, or pituitary disease. Its peak time of diagnosis at age 50 years is similar to the late time course for the development of gastric carcinoids and thymic carcinoid tumors in MEN 1 patients (14, 89). Similar to that recently reported with the development of thymic carcinoids (14), no clinical parameter, laboratory value, or other MEN 1 feature distinguished patients who did or did not develop a meningioma. Therefore, because it cannot be predicted which patient with MEN 1 will develop a meningioma, it will be necessary to perform routine brain MRIs to detect them. Because the youngest age any patient was first diagnosed with a meningioma in our study was 29 years old, we would recommend an initial brain MRI be performed by age 25 years. At present, we have insufficient data to propose when brain MRIs should be repeated if initially negative.

Previous studies in sporadic meningiomas show a high frequency (44–100%) of LOH on chromosome 22q12 at NF2 gene locus (35, 39, 44), and patients with NF2 develop meningiomas that have a high frequency of NF2 gene LOH (49). Our results from allelotyping of 22q12 in the MEN 1-associated meningioma show that there is no LOH on chromosome 22q12.
in the region of the NF2 gene. This data suggested that LOH of NF2 gene may not be involved in the tumorigenesis of MEN 1-associated meningioma.

Chromosome 1p LOH is the second most common chromosomal abnormality (28–57%) reported in sporadic meningiomas (39, 44–46, 46–48). The present study demonstrated that 1p LOH occurred at 6 of 12 loci on chromosome 1p examined in the MEN 1-related meningioma. Two tumor suppressor genes (p73 and ARHI/NOEY2) have been localized on 1p36 and 1p31, respectively (50, 53), and in our study, at each locus in the MEN 1-associated meningioma, LOH was found. ARHI/NOEY2 is a maternal imprinted tumor suppressor gene (53), and our data demonstrates that the paternal (functional) allele of ARHI/NOEY2 gene was lost in the MEN 1-associated meningioma. This means that ARHI/NOEY2 gene is completely inactivated in this meningioma, suggesting that loss of this tumor suppressor gene could be contributing to the tumorigenesis of the meningioma in MEN 1 patients. However, with the paternal imprinted gene p73 (51, 90), which is a homologue of p53 (51, 52, 91), loss of the paternal allele was found, indicating that the p73 gene might not be involved in the pathogenesis of meningioma in MEN 1 patients.

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References


Meningiomas in MEN 1

Meningiomas May Be a Component Tumor of Multiple Endocrine Neoplasia Type 1

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