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Pituitary adenomas in patients with multiple endocrine neoplasia type 1: a single-center experience in China

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Abstract

Purpose To explore the clinical characteristics of pituitary adenomas in patients with MEN1 and to summarize treatment strategies for MEN1 in a Chinese population.

Methods We retrospectively analyzed 54 MEN1 patients with pituitary adenomas diagnosed at Peking Union Medical College Hospital from March 2003 to January 2017. Clinical data, laboratory testing results, treatments of involved glands and treatment responses were collected and analyzed.

Results The mean age at pituitary adenoma diagnosis was 53.9 ± 17.8. The patients initially consulted the Endocrinology, General Surgery and Neurosurgery departments, in descending frequency. The nonfunctioning adenoma, prolactinoma, GH-secreting adenoma, cosecreting adenoma, and ACTH-secreting adenoma subtypes accounted for 48.1%, 27.8%, 9.3%, 9.3% and 5.6% of the cases, respectively. The remission rate for prolactinomas was 46.2% (6/13) treated with bromocriptine. And the remission rates were 87.5% (7/8) and 100% (3/3) for GH-secreting adenomas and ACTH-secreting adenomas respectively achieved by transsphenoidal surgery. Nineteen (35.2%) patients with asymptomatic nonfunctioning pituitary adenomas showed no progression after a 35-month follow-up with close observation. Regarding treatment priority, patients with thymic carcinoid tumors received first-line surgery, 54% of the patients with enteropancreatic tumors had these tumors treated first, and 26% of all patients had their pituitary adenomas treated first. In acromegalic patients, pituitary lesions tended to be treated first (75%, p = 0.002). PHPT and adrenocortical adenomas can be managed with elective surgery.

Conclusions The treatment of MEN1 requires cooperation between multidisciplinary teams. Individualized treatment according to the severity of glandular involvement is needed. GH-secreting and ACTH-secreting pituitary adenomas require active treatment, while nonfunctioning pituitary adenomas can be observed closely.

Keywords Multiple endocrine neoplasia type 1 · Pituitary adenoma · Treatment · Chinese population

Introduction

Multiple endocrine neoplasia (MEN) includes MEN type 1 and MEN type 2. The most common tumors are parathyroid hormone-secreting adenomas or gastrinomas in MEN1 and calcitonin-secreting or catecholamine-secreting tumors in MEN2 [1]. MEN1 is an autosomal dominant disorder caused by mutations in the *MEN1* gene locus on chromosome 11q13 [2, 3] and is characterized by tumors in two or more endocrine glands, such as the pituitary gland, parathyroid glands or pancreatic islets [4]. In addition, adrenocortical tumors, cutaneous lipomas, thymic/bronchial carcinoid tumors, facial angiofibromas, collagenomas and meningiomas can occur [1, 5]. The clinical manifestations of MEN1 are associated with abnormal levels of hormones secreted by the

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involved glands. Most patients have a family history, but 8–14% of MEN1 cases are sporadic cases [6, 7].

The prevalence of MEN1 is approximately 0.02–0.2 cases per 1000 people [8]. The percentage of pituitary adenomas varies from 10 to 76% among all MEN1 cases according to different study series [9–11]. Studies analyzing pituitary adenomas in MEN1 are few and have been reported only in European countries [12–15]. In Asian populations, a multicenter study described the baseline characteristics of MEN1 patients in Japan [16], and a study of 18 MEN1 patients in India was reported in 2016 [17]. However, the characteristics of pituitary adenomas in MEN1 were not discussed in those studies. In addition, to our knowledge, no case series or epidemiological studies describing the characteristics of pituitary adenomas in patients with MEN1 in Chinese populations have been published. As one of the largest pituitary disease registry centers in China, our center performed a total of 900 pituitary surgeries per year. Because the Endocrinology division at our center is capable of managing complicated endocrine tumors [18], we analyzed pituitary involvement in Chinese MEN1 patients from our center and attempted to provide insights into screening, target gland management and follow-up strategies for MEN1.

Materials and methods

Study population

A total of 171 patients were diagnosed with MEN1 at Peking Union Medical College Hospital (PUMCH) from March 2003 to January 2017. We retrospectively analyzed 54 MEN1 cases with pituitary lesions out of the total 171 MEN1 cases. The included cases met the diagnostic criteria for MEN1: the occurrence of two or more primary MEN1-associated endocrine tumors, for example, parathyroid adenoma, enteropancreatic tumor and pituitary adenoma; the occurrence of one MEN1-associated tumor in a first-degree relative of a patient with a clinical diagnosis of MEN1; or the identification of a germline MEN1 mutation [4]. In addition, all cases had pituitary involvement.

Pituitary adenomas are diagnosed based on endocrine symptoms caused by abnormally elevated anterior pituitary hormone levels and the detection of tumors by magnetic resonance imaging (MRI). Tumors with a diameter greater than 1 cm are defined as macroadenomas, while those with a diameter less than 1 cm are defined as microadenomas. Prolactinomas are diagnosed by elevated serum prolactin (PRL) levels (> 150 μg/ml) and the exclusion of other causes of hyperprolactinemia, and are confirmed by MRI [19]. The diagnosis of acromegaly is confirmed by elevated random serum growth hormone (GH) levels of > 1 ng/ml and nadir GH levels of > 0.4 ng/ml during an oral glucose tolerance test (OGTT) as well as by elevated serum insulin-like growth factor 1 (IGF-1) levels [20, 21]. Cushing's disease is diagnosed by an elevated adrenocorticotropic hormone (ACTH) level (> 20 ng/ml), the absence of cortisol suppression during a low-dose dexamethasone suppression test, and the suppression of cortisol during a high-dose dexamethasone suppression test, thus reflecting ACTH-dependent endogenous hypercortisolism. Patients with atypical laboratory test results or negative MRI results need further confirmation by inferior petrosal sinus sampling (IPSS), and a central/peripheral ACTH gradient of greater than three upon corticotrophin-releasing hormone stimulation helps to confirm the diagnosis [22, 23]. A diagnosis of nonfunctioning adenoma requires the presence of adenomas on MRI without an elevation in the levels of the relevant hormones [6, 13].

Primary hyperparathyroidism (PHPT), gastroenteropancreatic neuroendocrine tumors (GEP-NETs), thymic carcinoid tumors and adrenocortical adenomas were diagnosed according to the corresponding guidelines [6, 24–27].

The study was approved by the Ethics Committee of the PUMCH. Informed consent was obtained from each patient.

Data collection

The demographic characteristics, symptoms, time of symptom onset, time of diagnosis of MEN1, time of diagnosis of each involved endocrine gland, family history, comorbidities, laboratory test results, imaging findings, genetic information, medical and surgical management regimen, pathological subtypes of pituitary adenomas, pretreatment and posttreatment anterior pituitary hormone levels and enhanced MRI results of the sella and sphenoid were collected.

Genetic analysis

Genetic analysis is not a routine test required by a diagnosis of *MEN1* in our center. For patients with a family history or with a strong desire to be tested, peripheral blood was drawn, and the *MEN1* gene, including 9 coding exons and 16 splice junctions, was sequenced.

Follow-up

Patients who underwent pituitary surgery were scheduled for follow-up examinations at 3 months, 6 months and 1 year. The evaluation for pituitary adenomas should comprise clinical manifestations, relevant hormone tests and enhanced MRI of the pituitary. Subsequent follow-up was regularly conducted every 1–2 years.

The duration of follow-up refers to the time from the diagnosis of pituitary adenomas in MEN1 patients to the time of the last follow-up.

Statistical analysis

Data were analyzed by IBM SPSS Statistics 22 software (SPSS Inc., Chicago, IL, USA). Categorical variables are expressed as absolute numbers and percentages. Quantitative results are expressed as the means ± standard deviations and the medians plus ranges. Data were compared between groups using Chi square tests. Significant differences were determined by unpaired t tests when applicable. $p < 0.05$ was considered significant.

Results

Baseline characteristics

In our cohort, the male:female ratio was 1:1.08 (26:28). Eleven (20.4%) patients had a family history of MEN1. Sixteen (29.6%) patients were initially diagnosed with pituitary tumors. Twelve (22.2%) patients were initially diagnosed with PHPT. Twenty-four (44.4%) patients were initially diagnosed with enteropancreatic tumors. In addition, one (1.9%) patient was initially diagnosed with adrenocortical tumors, and one (1.9%) was initially diagnosed with ovarian teratomas. The mean age at diagnosis of MEN1 was 54.2 ± 17.2. The mean age at diagnosis of pituitary disease was 53.9 ± 17.8 (Table 1).

Genetic analysis

Six (11.1%) patients underwent genetic testing. Four of the six had mutations in the *MEN1* gene, while the other 2 were wild-type; thus, the mutation rate was 66.7%. Among the 6 tested patients, 2 had a family history of MEN1, and germline mutations were found in both of these patients. Four patients presented sporadic cases, and germline mutations of *MEN1* were found in 2 of these four patients (Table 1).

Distribution of endocrine lesions

Thirty-seven (68.5%) patients were found to have PHPT with the typical clinical manifestations of osteoporosis, renal calculus, hypercalcemia and hypophosphatemia. Twenty-nine (78.4%) of these patients received surgery to treat their PHPT. Enteropancreatic tumors were the most commonly presented lesions, accounting for 90.7% (48/54) of all patients (Fig. 1). Among the patients with enteropancreatic tumors, 23 (47.9%) had insulinoma, three (6.2%) had gastrinoma, and one (2.1%) was diagnosed with glucagonoma. The other 21 (43.8%) patients had nonfunctioning enteropancreatic neuroendocrine tumors. Twenty-eight (58.3%) of the patients with enteropancreatic tumors received surgery, and 3 (6.3%) received drug therapy. Among these patients, patients with insulinoma had a significantly higher surgery rate (86.9%, $p < 0.001$) than patients with any other type of enteropancreatic lesion. One (33.3%) patient with gastrinoma was treated with surgery, and one (33.3%) received drug therapy (octreotide). The patient with glucagonoma underwent surgery. Most (61.9%, 13/21) patients with nonfunctioning enteropancreatic neuroendocrine tumors received no treatment, whereas 6 (28.6%) had surgery and 2 (9.5%) received octreotide. Eighteen (33.3%) patients had adrenocortical tumors, and all adenomas in this patient group were nonfunctioning adenomas. Three (16.7%) patients with adrenocortical tumors underwent surgical tumor removal, four (7.4%) were reported to have lipomas, and two (3.7%) had thymic carcinoid tumors; both of these patients underwent surgery.

The distribution of the consultation departments initially visited by the MEN1 patients was as follows: Department of Endocrinology (57.4%, 31/54), Department of General Surgery (24.1%, 13/54), Department of Neurosurgery (14.8%, 8/54) and other departments (3.7%, 2/54). The eight patients who initially consulted the Department of Neurosurgery included 5 patients with acromegalic manifestations, 1 with severe symptoms of lactation and hyposexuality and 2 with symptoms caused by mass effect. Notably, patients with GH-secreting pituitary adenomas had a significantly higher rate (75%, $p = 0.001$) of initially visiting the Department of Neurosurgery than did patients with other subtypes of pituitary tumors (Table 1).

Subtypes of pituitary adenomas

In our cohort, 15 (27.8%) patients had prolactinomas, 5 (9.3%) patients had GH-secreting adenomas, 3 (5.5%) patients had ACTH-producing adenomas, 5 (9.3%) (5/54; 2/54 GH + PRL, 2/54 ACTH + PRL, 1/54 GH + ACTH) patients had cosecreting adenomas, and 26 (48.1%) patients had nonfunctioning pituitary adenomas (Fig. 2).

PRL-secreting adenomas

The male:female ratio of the 19 patients with PRL-secreting adenomas was 1.11:1 (10:9). Thirty (68.4%) of the patients presented with hyperprolactinemia-related clinical features, such as lactation, breast development, menstrual disorders and hyposexuality. Three (15.8%) patients showed symptoms such as headache, dizziness, visual impairment and visual field defects due to mass effect, and 2 of these 3 had pituitary tumors cosecreting GH. The median PRL level was 263 (range 153.7–1768) ng/ml. The median size of the pituitary lesion on MRI was 7.7 (range 1–48) mm. Three (15.8%) patients were classified as Knosp grade III or IV (2 of these 3 had GH-cosecreting tumors). Thirteen (68.4%) patients received bromocriptine as their first-line treatment

Table 1 Summary of demographics and clinical data for 54 MEN1 patients with pituitary adenomas

No.	Age	Sex	Department of initial consultation	Pituitary tumors	Treatment of pituitary lesions	PHPT	GEP-NET	Other glands involved	Management priority	Family history	Germline MEN1 mutation	Follow-up time (mo.)
1	29	F	Endocrinology	ACTH	Surgery	Yes	NF-NET	No	Pituitary	No	–	75
2	66	M	Endocrinology	ACTH	None	No	insulinoma	No	No treatment	No	–	12
3	42	F	Endocrinology	ACTH	None	Yes	NF-NET	Adrenocortical tumors	PHPT	Yes	Yes	8
4	33	F	Endocrinology	PRL	Bromocriptine	Yes	insulinoma	No	Pituitary	No	–	85
5	25	F	General surgery	PRL	None	No	NF-NET	Adrenocortical tumors	GEP-NET	No	–	72
6	32	M	Endocrinology	PRL	Bromocriptine	No	no	Adrenocortical tumors	Pituitary	No	No	70
7	31	F	Endocrinology	PRL	None	Yes	NF-NET	Thymic carcinoid	Thymic carcinoid	No	–	29
8	51	M	General surgery	PRL	None	Yes	insulinoma	Adrenocortical tumors	GEP-NET	No	–	26
9	51	M	Endocrinology	PRL	None	Yes	NF-NET	No	PHPT	No	–	18
10	37	F	Endocrinology	PRL	Bromocriptine	Yes	gastrinoma	No	pituitary	No	–	22
11	52	M	Endocrinology	PRL	Bromocriptine	Yes	insulinoma	No	GEP-NET	Yes	–	7
12	64	M	General surgery	PRL, ACTH	None	Yes	NF-NET	No	GEP-NET	Yes	–	85
13	54	M	Neurosurgery	PRL	Surgery	Yes	NF-NET	No	Pituitary	Yes	–	81
14	30	M	General surgery	PRL	Bromocriptine	Yes	insulinoma	No	GEP-NET	Yes	–	15
15	56	F	General surgery	PRL	Bromocriptine	Yes	insulinoma	Adrenocortical tumors	GEP-NET	No	–	113
16	25	M	Endocrinology	PRL	Bromocriptine	Yes	gastrinoma	No	Pituitary	Yes	Yes	60
17	51	F	Endocrinology	PRL	Bromocriptine	Yes	no	Adrenocortical tumors	Pituitary	No	Yes	33
18	45	F	Endocrinology	PRL, ACTH	Surgery	Yes	NF-NET	Adrenocortical tumors	GEP-NET	No	–	122
19	44	F	General surgery	PRL	None	Yes	insulinoma	Adrenocortical tumors	GEP-NET	No	–	16
20	59	F	Endocrinology	PRL	None	No	NF-NET	No	GEP-NET	No	–	8
21	40	M	General surgery	NF	None	Yes	insulinoma	No	GEP-NET	No	–	87
22	37	M	Endocrinology	NF	None	No	insulinoma	No	GEP-NET	No	–	83
23	64	F	Endocrinology	NF	None	Yes	NF-NET	Adrenocortical tumors	PHPT	No	–	77
24	26	F	Endocrinology	NF	None	Yes	insulinoma	No	GEP-NET	No	–	63
25	40	F	Endocrinology	NF	None	No	insulinoma	No	No treatment	No	–	55
26	51	F	Endocrinology	NF	None	Yes	NF-NET	Adrenocortical tumors	PHPT	No	–	62
27	49	M	Endocrinology	NF	None	Yes	NF-NET	No	PHPT	No	–	40
28	36	F	Endocrinology	NF	None	No	insulinoma	No	GEP-NET	No	–	27
29	14	F	Endocrinology	NF	None	No	insulinoma	No	GEP-NET	No	–	18
30	57	F	Endocrinology	NF	None	No	insulinoma	No	GEP-NET	No	–	17
31	35	F	Endocrinology	NF	None	Yes	insulinoma	No	GEP-NET	No	–	15
32	54	F	Endocrinology	NF	None	Yes	no	Adrenocortical tumors	No treatment	Yes	–	8
33	32	F	General surgery	NF	None	Yes	insulinoma	No	GEP-NET	No	–	36
34	47	M	Endocrinology	NF	None	No	insulinoma	No	GEP-NET	No	–	24

Table 1 (continued)

No.	Age	Sex	Department of initial consultation	Pituitary tumors	Treatment of pituitary lesions	PHPT	GEP-NET	Other glands involved	Management priority	Family history	Germline MEN1 mutation	Follow-up time (mo.)
35	42	F	Others	NF	None	Yes	NF-NET	Adrenocortical tumors	PHPT	Yes	–	18
36	27	M	Endocrinology	NF	None	No	insulinoma	No	GEP-NET	No	–	7
37	62	M	Others	NF	None	No	gastrinoma	No	GEP-NET	No	No	6
38	59	M	General surgery	NF	None	No	insulinoma	No	GEP-NET	No	–	21
39	44	M	Endocrinology	NF	None	Yes	insulinoma	No	GEP-NET	No	–	81
40	40	F	Neurosurgery	NF	Surgery	No	no	Adrenocortical tumors	Pituitary	Yes	–	85
41	36	M	General surgery	NF	None	Yes	glucagonoma	No	PHPT	No	–	43
42	39	M	Neurosurgery	NF	Surgery	Yes	NF-NET	No	PHPT	Yes	–	24
43	33	M	General surgery	NF	None	No	insulinoma	No	GEP-NET	No	–	35
44	43	M	Endocrinology	NF	None	Yes	NF-NET	Adrenocortical tumors	PHPT	Yes	–	21
45	69	F	Endocrinology	NF	None	Yes	NF-NET	No	No treatment	No	–	37
46	53	M	Endocrinology	NF	None	Yes	NF-NET	Thymic carcinoid	Thymic carcinoid	No	–	35
47	42	M	Neurosurgery	GH	Surgery	Yes	no	No	Pituitary	No	–	36
48	29	M	Neurosurgery	GH	Somatostatin, surgery	No	no	Adrenocortical tumors	Pituitary	No	Yes	47
49	52	F	Neurosurgery	GH, ACTH	Somatostatin, surgery	Yes	NF-NET	4	Pituitary	No	–	59
50	58	F	Neurosurgery	GH	Surgery	No	NF-NET	Adrenocortical tumors	GEP-NET	No	–	15
51	55	F	Endocrinology	GH	Surgery	Yes	NF-NET	Adrenocortical tumors	Pituitary	No	–	20
52	52	M	General surgery	GH, PRL	Surgery	Yes	NF-NET	No	GEP-NET	No	–	185
53	38	M	Neurosurgery	GH, PRL	Somatostatin, bromocriptine, surgery	Yes	NF-NET	Adrenocortical tumors	Pituitary	No	–	31
54	54	F	Neurosurgery	GH	Surgery	Yes	NF-NET	No	Pituitary	No	–	12

PHPT primary hyperthyroidism, *GEP-NET* gastroenteropancreatic neuroendocrine tumor, *NF-NET* nonfunctioning neuroendocrine tumor

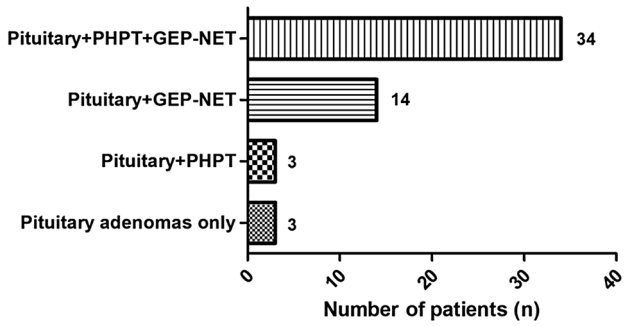

Fig. 1 Distribution of pituitary adenomas, PHPT and GEP-NET in 54 MEN1 patients. Of the 3 patients with pituitary lesions only, 2 had germline mutations in the MEN1 gene, and the other had a first-degree relative diagnosed with MEN1

regimen. Two (10.5%) patients underwent surgery because of the symptoms caused by ACTH and GH cosecretion. Four (21.1%) patients with mild clinical symptoms were observed and followed up, and the size of these pituitary adenomas did not increase during follow-up. Among the 13 patients treated with bromocriptine, 53.8% experienced symptomatic improvement, 46.2% experienced a decrease in the PRL level to within the normal range, 23.1% underwent subsequent surgery due to a poor response to bromocriptine, and 15.4% underwent surgery because of drug resistance (Fig. 2).

GH-secreting adenomas

Among the 8 patients with GH-secreting adenomas, the male:female ratio was 1:1 (4:4). All patients had typical acromegalic clinical manifestations, and six (75%) had headaches and visual field defects. The median level of random GH was 18.7 (range 5.6–154) ng/ml. The median lesion size on MRI was 26 (range 18–48) mm. Four (50%) patients were classified as Knosp grade III and above. In terms of complications, 3 (37.5%) patients were diagnosed with abnormal glucose metabolism. All patients received transsphenoidal surgery, and 2 (25.0%) received somatostatin injection after surgery. The GH level decreased to within the normal range 3 months after surgery in 87.5% of the patients. One (12.5%) patient did not recover and accepted γ-knife treatment 6 months later. The relapse rate was 14.3%, and the patient underwent another subsequent resection (Fig. 2).

ACTH-secreting adenomas

The male:female ratio was 1:2 (2:4). Four (66.7%) patients presented with symptoms of hypercortisolism. Cushing's disease was confirmed in all 6 patients by hormone testing. The median tumor size on MRI was 3 (range, 1–10) mm. Three (50%) patients underwent surgical resection, and all had remission of symptoms, with the cortisol level decreasing to within the normal range. One patient experienced

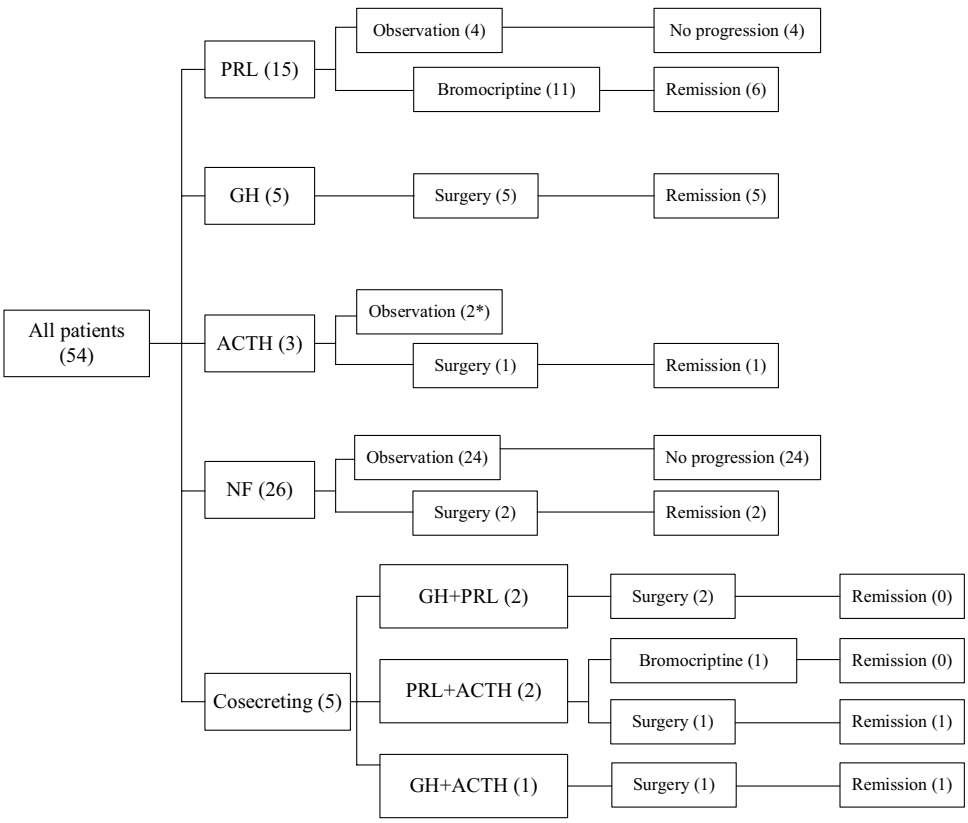

Fig. 2 Management and prognosis of pituitary adenomas in 54 MEN1 patients. Of the 2 patients with ACTH-secreting adenomas, 1 with mild clinical symptoms refused surgery, and no progression was found during follow-up. The other refused surgery and was lost to follow-up

recurrence 1 year later. Three (50%) patients did not undergo surgical treatment. Among these patients, 2 with mild clinical symptoms were closely observed during follow-up, and no progression was found. One patient refused surgery and was lost to follow-up (Fig. 2).

Cosecreting adenomas

Two patients were clinically diagnosed with mixed somatolactotrophic pituitary adenomas, one of whom was administered bromocriptine and somatostatin before resection. One of them showed no remission and received radiotherapy afterwards. The other was administered bromocriptine for elevated PRL level. Two patients were diagnosed with pituitary adenomas cosecreting PRL and ACTH, one of whom underwent surgery. After surgery, the PRL level of this patient remained elevated, and the patient was subsequently treated with bromocriptine. The other patient received bromocriptine and tested positive for Cushing's disease during follow-up hormone testing. One patient was clinically diagnosed with composite somatotroph-ACTH pituitary adenoma. The patient continued somatostatin therapy after surgery and experienced reduction in the GH level (Fig. 2).

Nonfunctioning pituitary adenomas

Twenty-six patients had nonfunctioning pituitary adenomas, with a male:female ratio of 1:1 (13:13). Four (15.4%) of these patients presented with symptoms of hyperprolactinemia, 3 (11.5%) had dizziness, headache, visual impairment and visual field defects, and the remaining 19 (73.1%) showed no symptoms and were diagnosed with pituitary microadenomas during MEN1 screening. The median lesion size on MRI was 4 (range 2–30) mm; 23 (88.5%) patients were classified as Knosp grade I or II, and 3 patients (11.5%) were classified as Knosp grade III and above. Two patients underwent and recovered from surgery. Of the 19 patients with asymptomatic microadenomas, no progression to macroadenomas was observed during the median follow-up of 35 (6–87) months (Fig. 2).

MEN1 treatment strategies

Both patients with thymic carcinoid tumors elected to undergo surgical removal of thymic tumors as a first-line therapy owing to severe symptoms and the potential for a fatal outcome. Regarding the treatment of tumors in other glands, we noticed that among the 48 patients with enteropancreatic tumors, especially patients with insulinoma (82.6%, $p < 0.001$), 54.2% gave priority treatment to the enteropancreatic lesions. Fourteen (25.9%) patients gave priority treatment to the pituitary lesions. Among these 14 patients, 1 had an ACTH-secreting adenoma, 6 had prolactinomas, 6 had GH-secreting adenomas and 1 had a nonfunctioning pituitary adenoma. Patients with GH-secreting adenomas tended to give priority treatment to pituitary lesions (75%, $p = 0.002$); however, only 33.3% of the patients with prolactinomas, 35.3% of the patients with ACTH-secreting adenomas and 3.8% of the patients with nonfunctioning adenomas gave priority treatment to pituitary lesions. None of the 14 patients had thymic carcinoid tumors. Only 1 patient had an insulinoma, 2 patients had gastrinomas, 6 patients had nonfunctioning neuroendocrine tumors, and 5 patients had no involvement of gastroenteropancreatic glands. For most PHPT patients without severe symptoms, parathyroidectomy was an elective surgery. No preference was observed in the treatment priority of patients with either PHPT or nonfunctioning adrenocortical adenoma (Table 1).

Follow-up

The median follow-up duration was 34 (6–185) months. One (1.9%) patient died of thymic carcinoid tumor. Four (7.4%) patients were lost to follow-up. The median follow-up duration for patients with functioning pituitary tumors was 33 (7–185) months, while the median follow-up duration for patients with nonfunctioning pituitary adenomas was 35 (6–87) months (Table 1).

Discussion

MEN1 is a rare disease and involves multiple endocrine glands. The literature indicates that the pituitary gland is the third most frequently involved gland after parathyroid glands and pancreatic islets [6, 28]. However, consensus on the treatment of pituitary adenomas in patients with MEN1 has not yet been reached. Because of the multiple glands involved and the rarity of the disease, MEN1 can be overlooked due to a lack of awareness. Thus, the diagnosis and treatment of MEN1 requires cooperation between multiple departments. The Department of Endocrinology in our center, which serves as a key laboratory of endocrine research for the Chinese Ministry of Public Health, is experienced in managing rare and complicated endocrine disorders and has cooperated with the Departments of Neurosurgery, General Surgery, Chest Surgery and Urinary Surgery as a part of multidisciplinary teams (MDTs) in the management of MEN1. In our series, patients who consulted the Department of Endocrinology had a thorough screening of the pituitary gland, pancreas and parathyroid glands as well as other related glands, and the involved gland was then treated in the corresponding surgical department [18]. In our study, the department of initial consultation was most often the Department of Endocrinology. Thus, the rate of

missed diagnosis, especially regarding the detection of nonfunctioning neuroendocrine tumors, was reduced as much as possible, and patients were managed in a more efficient and individualized way.

We first reported the clinical characteristics of MEN1 patients in a Chinese population. Compared to the populations in the three existing large case series from France/Belgium, Italy and Japan, the Chinese population showed some distinct features (Table 2) [12, 14, 28]. The average onset age of pituitary tumors varied from 34.4 to 46.1 in the other three studies, which was in overall agreement with the data from our center (53.9 ± 17.8). However, we noticed a significantly higher prevalence of enteropancreatic tumors (approximately 90%) in our cohort than in the cohorts from other studies, in which the reported prevalence was approximately 47–62.4% [12, 14, 28]. The unpredictable high prevalence originated in part from the dominance of the Department of General Surgery, which manages complicated pancreatic surgeries, in our center [29, 30]. Additionally, the thorough screening of nonfunctioning enteropancreatic neuroendocrine tumors can explain the high prevalence. In our study, the incidence of PHPT was only 68.5%, much lower than the incidence of approximately 90% seen in studies of data from other centers. According to Han and Yan, the incidence of PHPT is lower in Asian populations than in Caucasian populations, which can explain the lower incidence we observed in the MEN1 patients [31, 32]. The proportions of patients with combined involvement of the pancreas, parathyroid glands and pituitary gland were 41.9%, 51.7%, 59.8% and 63.0% in the studies by Verges et al., Giusti et al., Sakurai et al. and us, respectively [12, 14, 28]. This proportion was considerably higher in Asian populations; the ethnic difference may account for this discrepancy (Table 2). Among the 6 patients who underwent genetic testing, germline mutations in *MEN1* were detected in 100% of the patients with a family history and in 50% of the patients with sporadic cases. This result was consistent with those observed in previous studies, which showed mutation rates of greater than 90% in familial cases and 50–60% in sporadic MEN1 cases [14, 28].

To our knowledge, our study was the first to describe the treatment strategy and order of management of each involved gland. The overall treatment principle for MEN1 is based on the severity of glandular involvement. Thus, the target gland producing the most severe symptoms or potential consequences should receive priority treatment. In addition, the order of diagnosis of each gland should be considered. In our cohort, thymic tumors were the most urgent treatment priority, considering the potential disastrous outcome [33, 34]. The second most urgent priority was enteropancreatic tumors, especially insulinomas, because of their life-threatening symptoms [6, 35, 36]. Functioning pituitary adenomas were usually considered the third most urgent priority. Surgeries to treat PHPT and nonfunctioning

Table 2 Literature review of pituitary adenomas in MEN1 patients

Author/year	Country	Total MEN1 patients (n)	Pituitary adenoma (n)	Age at diagnosis of pituitary adenoma	Male:female ratio	PHPT (%)	GEP-NET (%)	Pituitary + PHPT + GEP-NET (%)	Type of pituitary adenomas					Size of pituitary adenomas	
									PRL (%)	GH (%)	ACTH (%)	Cosecreting adenomas (%)	NF (%)	Macroadenomas	Microadenomas
Verges, 2002	France & Belgium	324	136	38 ± 15.3 (12–83)	1:2.24 (42:94)	123 (90.4)	64 (47.1)	57 (41.9)	85 (62.5)	12 (8.8)	6 (4.4)	7 (9.6)	20 (14.7)	116 (85.0)	20 (15.0)
Giusti, 2017	Italy	475	178	34.4 ± 14.7 (13–59)	1.44:1 (105:73)	163 (91.6)	100 (56.2)	92 (51.7)	120 (67.4)	12 (6.8)	8 (4.4)	2 (1.2)	36 (20.2)	66 (37.1)	112 (62.9)
Sakurai, 2012	Japan	536	266	46.1 ± 14.4 (11–75)	–*	257 (96.6)	166 (62.4)	159 (59.8)	97 (36.5)	34 (12.9)	10 (3.8)	24 (9.0)	67 (28.2)	–*	–*
Our study, 2018	China	171	54	53.9 ± 17.8 (17–65)	1:1.08 (26:28)	37 (68.5)	49 (90.7)	34 (63.0)	15 (27.8)	5 (9.3)	3 (5.6)	5 (9.3)	26 (48.1)	10 (18.5)	44 (91.5)

*Not described in the study

adrenocortical adenomas could be addressed more flexibly. Fourteen patients who gave priority treatment to pituitary lesions were mainly diagnosed with functioning pituitary adenomas, especially acromegaly, and treated these lesions first because of severe clinical symptoms and potential comorbidities. We noticed that none of the 14 patients had thymic carcinoid tumors, and only 1 patient who was also diagnosed with insulinoma chose to treat prolactinoma first. Thus, we recommend that MEN1 patients should treat thymic and enteropancreatic tumors (especially insulinomas) first after diagnosis and that the treatment of pituitary adenomas is the second priority. In addition, functioning pituitary adenomas, especially GH-secreting and ACTH-secreting adenomas, need early management. Parathyroid and adrenal cortical lesions can be managed with flexibility because of their noninvasive and nonfatal characteristics.

Regarding the subtypes of pituitary tumors, the proportions of PRL-secreting, GH-secreting, ACTH-secreting, cosecreting and nonfunctioning adenomas were 27.8%, 9.3%, 5.6%, 9.3% and 48.1%, respectively, in our study. PRL-secreting adenomas were the most common pituitary lesion found in the European studies [12, 24], but the prevalence of this lesion was only 27.8% in our study, which paralleled the findings of Sakurai's study [28]. And notably we showed a high prevalence of nonfunctioning pituitary adenoma. We thought that thorough screening of pituitary adenomas in patients with MEN1 was the reason for that. In our center, each patient diagnosed with MEN1 was screened for endocrine lesions carefully at the Department of Endocrinology. And enhanced MRI was applied for the assessment of pituitary lesion. Therefore with high sensitivity and detection rate, we had 48.1% of patients diagnosed with nonfunctioning pituitary adenomas, and 35.2% of them were nonfunctioning microadenomas diagnosed by screening. Cosecreting pituitary adenomas are more often seen in MEN1 patients, and this finding is particularly true for adenomas secreting both PRL and ACTH, which are highly unusual [37, 38]. Notably, our study showed a prevalence of cosecreting pituitary adenomas of 9.3% (Table 2). Nonfunctioning adenomas, which accounted for 48.1% of the MEN1 patients with pituitary adenomas, were the most frequent subtype seen in our center; most of these were microadenomas diagnosed via MEN1 screening.

Current treatments for different types of pituitary adenomas are generally similar to those for the corresponding tumors occurring in non-MEN1 patients [4]. Surgery is the first-line treatment for GH-secreting and ACTH-secreting adenomas. Prolactinomas can be treated with dopamine agonists or surgery according to the tumor size and form or the patient's preference. Previous studies reported that pituitary tumors were more aggressive in MEN1 patients than in patients without MEN1 [11, 14, 37]. Pituitary tumors present more frequently as macroadenomas and exhibit lower response rates to treatment in MEN1 patients than in non-MEN1 patients [14, 37]. However, in our study, 81.5% of the pituitary adenomas were classified as Knosp grades 0-II, and only 18.5% were Knosp grades III or IV. We attribute these proportions to the abundance of nonfunctioning microadenomas diagnosed among our cohort. Regarding treatment response, the remission rates for functioning pituitary adenomas in our center agreed with the data reported by other large-scale studies conducted in non-MEN1 patients with pituitary adenomas [39–42]. Nonfunctioning microadenomas constituted approximately 35.2% of the pituitary tumors found in MEN1 patients. Furthermore, in our study, no progression to macroadenomas was observed in any of the 19 patients with asymptomatic pituitary microadenomas; this finding was consistent with that of the cohort study performed by de Laat et al. and suggested the possible indolent behavior of these tumors [13, 43]. Overall, the results of our study suggested that pituitary adenomas in MEN1 patients are not as aggressive as previously believed and that acceptable remission rates can be achieved via active treatment.

In conclusion, MEN1 is a complicated disease involving multiple endocrine glands. MDTs are required for diagnosis and proper treatment. Individualized treatment for MEN1 patients according to the severity of glandular involvement is needed. The relevant departments must treat MEN with great importance to prevent missed diagnoses and treatment delays. In MEN1 patients, functioning pituitary adenomas, especially acromegaly and Cushing's disease, require active treatment, while nonfunctioning pituitary adenomas can be observed closely.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

Ethical approval This study was performed in accordance with the ethical standards of the Institutional Ethics Committee of Peking Union Medical College Hospital at the Chinese Academy of Medical Sciences & Peking Union Medical College and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Written or verbal informed consent was obtained from all individual participants included in the study.

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