

CLINICAL STUDY

Gender-related differences in MEN1 lesion occurrence and diagnosis: a cohort study of 734 cases from the Groupe d'étude des Tumeurs Endocrines

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Abstract

Context: Multiple endocrine neoplasia type 1 (MEN1) disease is an autosomal dominant syndrome that is believed to equally affect men and women. This assumption has never been confirmed.

Objective: The aims of this study were to evaluate the impact of gender on the prevalence of MEN1 lesions, on their lifetime probability of occurrence, and on the diagnosis of MEN1.

Design: Data regarding a study of 734 cases of MEN1 from the multicenter 'Groupe d'étude des Tumeurs Endocrines' were analyzed.

Results: There were 57.8% females. The prevalence and probability of pancreatic tumors were higher in males than in females ($P=0.06$, $P=0.0004$). This difference was due to gastrinomas. The prevalence and probability of developing pituitary tumors were significantly greater in females ($P<0.001$, $P<0.0001$). Thymic tumors were exclusively found in men. There were no significant gender differences in the prevalence and the probability of developing hyperparathyroidism, or adrenal and bronchial tumors, or in the proportion of positive genetic tests. A family history of MEN1 was more frequently found in men than in women at the time of diagnosis ($P=0.02$). In the case of pituitary tumor, the proportion of patients diagnosed with MEN1 at the time of the first lesion was lower in women (44.2%) than in men (67.3%).

Conclusion: The phenotype expression of the MEN1 disease gene was different in males and females. In female patients, the possibility of MEN1 is not sufficiently taken into account. Any patient presenting a lesion that belongs to the MEN1 spectrum, such as a pituitary tumor, should be closely questioned about their family history and should be tested for hypercalcemia.

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Introduction

Multiple endocrine neoplasia type 1 (MEN1) is an inherited disease that predisposes carriers to primary hyperparathyroidism (pHPT), endocrine enteropancreatic tumors, pituitary tumors, and adrenal and thymic/bronchial neuroendocrine tumors (th-NET/br-NET).

MEN1 disease may display various clinical associations, and the criteria for diagnosis were established in Italy (Gubbio) during an international MEN meeting and are regularly updated (1–3). Most cases occur in the setting of a family history of MEN1, but sporadic cases of MEN1 are encountered. MEN1 mutations are found in most MEN1 patients but not in all. Indeed, up to 15% of index

cases for familial MEN1 fail to yield a germline mutation; this may be the result of alterations in regulatory or UTRs of the *MEN1* gene or possibly genes other than MEN1 causing the disease (4). The *MEN1* gene is an ~10 kb gene located on chromosome 11q13, which encodes menin (5). MEN1 disease is usually described as an autosomal dominant cancer syndrome with very high penetrance and a similar distribution in men and women (6). Nevertheless, studies focusing on MEN1-related th-NET, largely confined to men, show the importance of gender in at least this type of lesion (7–10). There are large variations between studies in the sex ratio, depending on the center, the population size, and the type of lesion studied. Several cohort studies that did not focus on specific lesions suggested an overall female predominance of about 52–56% of MEN1 patients (11, 12). In contrast, studies that focus on specific lesions provided discordant sex ratios with a proportion of females ranging, for example, from 36 to 58% in MEN1 patients with Zollinger–Ellison syndrome (ZES) (13–16). Several years ago, the Groupe d'étude des Tumeurs Endocrines (GTE) already pointed out the higher prevalence of pituitary lesions in women than in men (17). To our knowledge, no systematic evaluation of gender differences in the phenotype expression of MEN1 disease has yet been conducted. This prompted us to carry out a comprehensive analysis on this topic using a large unselected population of 734 MEN1 patients from the multicenter GTE network. These patients were precisely defined in accordance with international guidelines, were regularly followed up, and presented either a familial background or were sporadic cases (1–3, 18). Therefore, the inclusion of MEN1 patients in the database was not dependent on a single center or on a particular lesion-dependent aspect of the disease. The aims of this study were to evaluate the impact of gender on the prevalence of every MEN1 lesion, on their lifetime probability of occurrence, and finally on the time to the diagnosis of MEN1.

Population and methods

The study population comprised of 734 MEN1 patients presenting at least one MEN1 lesion and registered in the GTE database. The GTE network for MEN1, created in February 1991, includes clinical centers that are scattered in the 22 regions of France and in Belgium associated with the four genetics departments in charge of the diagnosis. Data from MEN1 patients diagnosed and regularly followed from 1956 to 1991 in the clinical departments involved in the management of MEN1 patients were incorporated into the GTE database in 1991. Since 1991, GTE members have been required to declare new cases for inclusion in the national MEN1 database. Moreover, the genetics departments regularly detect new cases and family trees are established for all

familial cases. They are also used to identify affected family members.

To be included in the study, patients had to fulfill specific diagnosis criteria in accordance with international guidelines (1–3): i) patients with a MEN1 mutation and presenting at least one of the following symptomatic or silent lesions: pHPT, pancreatic, or duodenal endocrine tumor; pituitary tumor; adrenal tumor; th-NET; br-NET; and gastric enterochromaffin-like tumor (ECLoma). ii) Patients belonging to a known MEN1 family (at least one first-degree relative affected) and presenting at least one of the aforementioned lesions. iii) Patients without positive genetic testing or a family background presenting at least two of the three major MEN1 lesions (pHPT, pancreatic, or duodenal endocrine tumor, pituitary tumor). This last category includes 73 patients. They were considered with caution and selected after a critical case-by-case analysis following rules already published by the GTE group (19). Criteria for the diagnosis of MEN1 lesions have evolved over the study period since the first cases were registered in the fifties. Before the parathormone (PTH) dosage era, the diagnosis of pHPT was usually based on clinical symptoms related to the presence of urinary lithiasis associated to the presence of hypercalcemia with or without hypophosphatemia in relation with a multiglandular disease or occurring in an already known MEN1 family. Later on, pHPT was defined as the association of hypercalcemia with elevated or inappropriate PTH levels after ruling out vitamin D insufficiency. ZES was diagnosed on a clinical and/or pathological basis (gastrinoma) before the introduction of biological criteria. Biological criteria used for the diagnosis of ZES were based on the measurement of gastrin concentration and gastric acid secretion without and with dynamic secretory tests (secretin) (20). Recently, additional criteria also tend to be used when concomitant proton pump inhibitors (PPI) cannot be interrupted. A serum gastrin concentration >1000 pg/ml in the presence of acidic gastric juice (pH < 2) confirms a diagnosis of ZES. Confirmed diagnosis of insulinoma was based on the association of fasting hypoglycemia associated with inappropriate secretion of insulin, C-peptide, or pro-insulin (21). The diagnosis of glucagonoma, VIPoma, or somatostatinoma was based on specific clinical symptoms and/or a peptide level repeatedly exceeding twice the upper limit of the normal range (22). The diagnosis of non-secreting pancreatic tumor (NSPT), pituitary tumor, adrenal tumor, th-NET, and br-NET has evolved over time since computed tomography (CT) became largely available in the 1980s, endoscopic ultrasound (EUS) and magnetic resonance imaging (MRI) in the 1990s. Moreover, the diagnosis performance of these imaging tools has improved steadily.

The 'first lesion' was defined as the lesion that was discovered first, whatever the other possible MEN1-associated lesions discovered during the following days

or weeks. The patient's age at the onset of a clinical feature was the age at the time of diagnosis for this feature. A patient was considered to have a family history of MEN1 when another MEN1 case was discovered or highly suspected in the same family during the pre-diagnosis period. Genetic analysis of the MEN1 sequence was performed in 583 cases (23). Families with a common ancestor were considered a single family, and all known affected members of each family were included. The mutations were recorded in the database. The study was approved by the ethics committee of Lyon University Hospital, and genetic studies were performed after informed consent had been provided by each patient, according to French and Belgian laws.

The referent physician provided initial data for the patient. A copy of each patient's file was obtained and stored in the Department of Epidemiology of Burgundy School of Medicine. A computerized recording file (CRF)

Table 1 Prevalence of MEN1 characteristics in males and females.

Characteristics of MEN1	Males n (%)	Females n (%)	P*
Number of patients	310 (42.2)	424 (57.8)	
Prevalence of lesions			
Hyperparathyroidism	287 (92.6)	394 (92.9)	0.859
Duodeno-pancreatic tumors	189 (61.0)	229 (54.0)	0.060
ZES/gastrinomas	113 (36.5)	103 (24.3)	<0.001
NSPT	43 (13.9)	70 (16.5)	0.328
Insulinomas	28 (9.0)	51 (12.0)	0.196
GVS	13 (4.2)	12 (2.8)	0.314
Pituitary tumors	94 (30.3)	197 (46.5)	<0.001
Prolactinomas	47 (15.2)	108 (25.5)	0.001
Other adenomas	47 (15.2)	89 (21.0)	0.045
Adrenal tumors	59 (19.0)	76 (17.9)	0.702
Bronchial tumors	10 (3.2)	13 (3.1)	0.902
Thymic tumors	19 (6.1)	0 (0.0)	<0.001
First lesion diagnosed ^a			
Hyperparathyroidism	70.0	63.0	0.047
Duodeno-pancreatic tumors	39.0	27.4	0.001
Pituitary tumors	17.7	30.4	<0.001
Adrenal tumors	4.8	4.3	0.702
Bronchial tumors	0.7	1.4	0.321
Thymic tumors	1.6	0.0	0.009
Number of lesions at MEN1 diagnosis			0.806
One	136 (43.9)	177 (41.8)	
Two	132 (42.6)	184 (43.4)	
Three and more	42 (13.6)	63 (14.9)	
Family history			0.023
Yes	249 (80.3)	307 (72.4)	
No	58 (18.7)	115 (27.1)	
Unknown	3 (1.0)	2 (0.5)	
Genetic mutation			0.169
Yes	223 (71.9)	279 (65.8)	
No	28 (9.0)	53 (12.5)	
Not analyzed	59 (19.0)	92 (21.7)	

*P value for comparison between genders by χ^2 test or exact Fisher test with 1 ddl for binary variables (prevalence of lesions, first lesion diagnosed), 2 or 3 ddl for categorical variables. ZES/gastrinomas, Zollinger–Ellison syndrome and/or gastrinomas; NSPT, nonsecreting pancreatic tumors; GVS, glucagonomas, VIPomas, somatostatinomas.

^aPercentage of patients presenting the lesion as the first one. The total percentage exceeds 100% because two or more lesions could be simultaneously diagnosed.

was created and filled in. This CRF comprised the following sections: identification data, pancreas gland, parathyroid glands, pituitary gland, adrenal glands, other endocrine tumors, thyroid, associated diseases, genetics, and follow-up. For each lesion, the date of occurrence, biochemical and imaging tests, medical and surgical treatments, and pathological reports were noted and then recorded in a computerized file. From copies of the patients' medical files, information was collected on a regular basis and data were updated. According to international recommendations, patients should be followed-up on a regular yearly basis (2). When data were missing or considered imprecise, an additional query form was sent to the physician in charge of the patient. The main centers were regularly visited by the surgeon in charge of the database (P G). Overall, 734 symptomatic patients (310 males and 424 females) were diagnosed between 1956 and 2005. Of the total patients, 217 were diagnosed before 1990 (30%), 161 from 1990 to 1995 (22%), and 356 after 1995 (48%). Before 1980, 62 patients were diagnosed (8%). The median age at the time of MEN1 diagnosis was 39.0 years (interquartile range 28.1–47.5 years) in males and 38.8 years (interquartile range 27.9–50.4 years) in females ($P=0.21$). pHPT was present in 93% of the patients, a duodeno-pancreatic tumor in 57%, and a pituitary tumor in 40%. As far as the study period of MEN1 diagnosis was concerned (<1990, 1990–1995, ≥ 1995), there was a drop in the prevalence of duodeno-pancreatic tumors (76%, 51%, 48% ($P<0.001$)) but no change in the prevalence of either pHPT (92%, 94%, 92% ($P=0.7$)) or pituitary tumors (43%, 44%, 36% ($P=0.1$)). These periods of diagnosis corresponded to changes in diagnostic and therapeutic strategies (progressive use of CT, MRI, EUS, and PPI): 54% of the patients diagnosed before 1990, 81% of the patients diagnosed during the 1990–1995 period, and 94% of those diagnosed thereafter benefited from genetic testing ($P<0.001$). A total of 84% of the patients presented either a genetic mutation and/or were members of an MEN1 family. Follow-up data were available for 721 patients (98.2%). The median follow-up time after MEN1 diagnosis was 6.1 years (interquartile range 2.3–10.3 years) in males and 6.7 years (interquartile range 2.3–10.7 years) in females ($P=0.32$), and 104 patients died (14%).

Statistical analysis

Descriptive results by gender are expressed as percentages for qualitative covariates, or as medians (interquartile range) for quantitative variables. Pearson's χ^2 test, Fischer's exact tests, or Kruskal–Wallis tests were used when appropriate. The following clinical lesions were studied: parathyroid lesions, pituitary tumors, adrenal tumors, br-NET, th-NET, ZES/gastrinomas, insulinomas, NSPT, and a pooled group of glucagonoma, VIPoma, and somatostatinoma. The period of

observation regarding the occurrence of each MEN1 lesion was calculated from the date of birth to the date of diagnosis of the lesion, or to the last information/death. The probability of occurrence was estimated using the Kaplan–Meier method, and cumulative probabilities of occurrence were calculated at 20, 40, and 60 years for each gender. Gender differences were tested using the log-rank test. Multivariate logistic regressions were used to examine whether gender was an independent risk factor for MEN1 diagnosis at the time of the first lesion, after adjustment for age, diagnosis period, and a family history of MEN1. This analysis was first performed in all patients irrespective of the site of the first lesion and then by subgroups of patients defined by the site of the first lesion. For all analyses, a *P* value below 0.05 was considered significant. Stata software, version 9.0 (Stata Corp., College Station, TX, USA) and SAS software, version 9.1 (SAS Institute, Inc., Cary, NC, USA), were used for statistical analyses.

Results

The majority of the patients was females (57.8%). The main characteristics of MEN1 according to gender are presented in Tables 1 and 2. The prevalence of pHPT, br-NET, and adrenal tumors was similar in both sexes. These results held true with regard to the probability of the occurrence of adrenal tumors and br-NET. Nevertheless, the probability of pHPT occurring was slightly higher in men (log-rank test: *P*=0.094). Th-NET was found exclusively in men. As far as the duodeno-pancreas was concerned, there was a significant male predominance in terms of prevalence and probability of ZES/gastrinomas, but there was no gender-related difference for other duodeno-pancreatic tumors. As described in Table 2 and illustrated in Fig. 1, the probability of developing a ZES/gastrinomas at 60 years was 54.9% in men and only 32.5% in women. The absolute risk for ZES/gastrinomas increases much more in men than in women during their lifetime, with a 7.6% difference at the age of 40 years and a 22.4% difference at the age of 60 years. Conversely, there was a significant female predominance for pituitary tumors both in terms of prevalence and in terms of probability regardless of age. A family history of MEN1 was more frequently observed in men than in women, whereas no significant difference was found among genders for positive genetic testing.

Irrespective of the lesion site, the proportion of patients diagnosed with MEN1 at the time of the first lesion was significantly higher in men (61.0%) than in women (53.1%) (Table 3). However, after adjustment for age, diagnosis period, and a family history of MEN1, female gender was only marginally associated with a delayed diagnosis of MEN1 (female gender odds ratio (OR): 0.77, 95% confidence interval (95% CI): 0.57–1.06, *P*=0.11). In the subgroup of patients

Table 2 Probability of occurrence of the various MEN type 1 lesions according to age of patients.

	Males Prob. (95% CI) ^b			Females Prob. (95% CI) ^b			<i>P</i> ^a
	20 years	40 years	60 years	20 years	40 years	60 years	
Hyperparathyroidism	13.0 (9.7–17.2)	55.6 (50.1–61.2)	91.6 (87.9–94.5)	10.0 (7.5–13.3)	51.2 (46.5–56.1)	88.0 (84.6–91.0)	0.09
Duodeno-pancreatic tumors	4.6 (2.8–7.7)	33.0 (27.7–38.9)	74.4 (67.9–80.5)	3.6 (2.2–5.9)	29.0 (24.6–33.9)	61.5 (55.8–67.3)	0.0004
ZES/gastrinomas	0.7 (0.2–2.6)	18.8 (14.4–24.3)	54.9 (47.2–63.0)	1.0 (0.4–2.5)	11.2 (8.3–15.0)	32.5 (26.8–39.1)	<0.0001
Insulinomas	2.6 (1.3–5.2)	6.5 (4.1–10.2)	12.4 (8.2–18.6)	1.9 (1.0–3.8)	8.7 (6.2–12.1)	15.7 (11.8–20.6)	0.35
GVS	0.7 (0.2–2.6)	3.5 (1.8–6.7)	5.5 (3.1–9.7)	0.2 (0.0–1.7)	2.1 (1.0–4.3)	4.7 (2.6–8.5)	0.23
NSPT	1.6 (0.7–3.9)	8.8 (6.0–12.9)	19.5 (14.2–26.6)	1.0 (0.4–2.5)	9.9 (7.2–13.5)	21.2 (16.4–27.1)	0.80
Other tumors	0.7 (0.2–2.6)	4.3 (2.4–7.6)	9.9 (5.8–16.5)	0.0	3.2 (1.8–5.7)	7.9 (5.0–12.4)	0.31
Pituitary tumors	3.3 (1.8–6.1)	24.2 (19.5–29.9)	42.6 (35.1–51.1)	6.7 (4.7–9.6)	31.4 (26.9–36.3)	53.4 (47.7–59.4)	0.001
Prolactinomas	2.3 (1.1–4.9)	14.1 (10.3–19.1)	22.8 (16.8–30.4)	4.9 (3.2–7.4)	21.8 (17.9–26.5)	30.7 (25.7–36.4)	0.002
Other adenomas	1.0 (0.3–3.1)	11.8 (8.3–16.7)	25.7 (18.6–35.0)	2.0 (1.0–3.9)	12.2 (9.1–16.3)	30.7 (25.7–36.4)	0.15
Adrenal lesions	0.3 (0.1–2.3)	9.5 (6.4–14.0)	32.5 (25.0–41.5)	0.2 (0.0–1.7)	5.8 (3.8–8.9)	25.0 (19.7–31.4)	0.14
Bronchial tumors	0.0	0.4 (0.1–3.1)	7.4 (3.6–14.9)	0.0	0.9 (0.3–2.6)	4.0 (2.0–8.0)	0.52
Thymic tumors	0.3 (0.1–2.3)	3.3 (1.6–6.4)	9.6 (5.9–15.4)	0.0	0.0	0.0	<0.0001

ZES/gastrinomas, Zollinger–Ellison syndrome and/or gastrinomas; GVS, glucagonomas, VIPomas, somatostatinomas; NSPT, nonsecreting pancreatic tumors.

^aComparison between genders of lifetime probability of lesion occurrence using log-rank test.

^bProbability of lesion occurrence expressed as % (95% confidence interval).

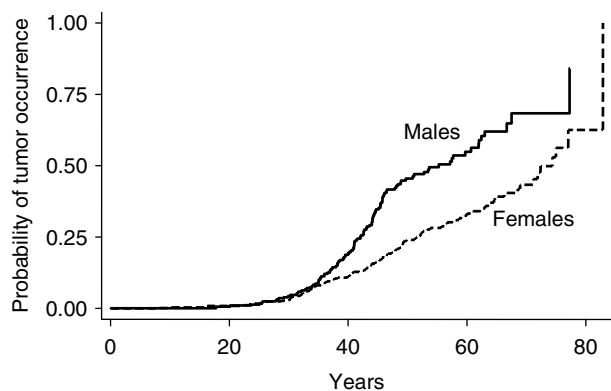


Figure 1 Probability of gastrinoma occurrence by gender according to age of patients.

whose first lesion was pituitary tumor, the proportion of those diagnosed with MEN1 at the same time was considerably higher in men (67.3%) than in women (44.2%). Adjustment for age, diagnosis period, and a family history of MEN1 did not alter this finding (female gender OR: 0.35, 95% CI: 0.17–0.71; $P=0.003$). However, further adjustment for the number of initial lesions reduced the gender difference (female gender OR: 0.51, 95% CI: 0.19–1.35, $P=0.18$). Whether the multivariate analysis was performed on the whole sample or restricted to patients with pituitary tumors as the first lesion, age <20 years, and a family history of MEN1 were strong predictors of an immediate diagnosis of MEN1, whereas the period of diagnosis was not. There were no significant gender differences regarding the diagnosis of MEN1 in analyses restricted to patients with pHPT, pancreatic tumors, or other tumors as the first lesions.

For the 320 patients not diagnosed with MEN1 at the occurrence of the first lesion, the time between the first lesion and the diagnosis of MEN1 was slightly longer in females (median time lag: 4.0 years, interquartile range 1.0–9.2 years) than in males (median time lag: 2.2 years, interquartile range 0.4–9.0 years) but not significantly so ($P=0.14$; Table 4). The analysis restricted to 89 patients with pancreatic tumors as the first lesion showed that the diagnosis of MEN1 was significantly ($P=0.04$) delayed in females (median time lag: 3.1 years, interquartile range 1.0–6.0 years) compared with males (median time lag: 1.3 years, interquartile range 0.3–3.9 years). There was no significant difference between women and men in the delay to MEN1 diagnosis when the first lesions were pituitary tumors, pHPT or other tumors.

Discussion

MEN1 disease is usually described as an autosomal dominant cancer syndrome with very high penetrance, which affects both genders equally (2, 3). For the first

time, this present comprehensive study shows the overall predominance of female patients in MEN1 disease and highlights the importance of gender in the phenotype expression of various MEN1 lesions. We demonstrated the greater lifetime likelihood of developing ZES/gastrinomas in men and of developing pituitary tumors in women. In contrast, both genders have a similar and very high probability of developing pHPT whereas, as expected, th-NET occurred mostly in men (7–10). Furthermore, the diagnosis of MEN1 tended to be delayed in women, especially when pituitary tumors, and to some extent duodeno-pancreatic tumors, were the first lesions to occur in the course of the disease.

A major strength of this comprehensive clinical study was to use well-defined diagnosis criteria in accordance with international guidelines established after the Gubbio meeting (1). These guidelines are used in all French and Belgian hospital departments likely to be involved in the management of MEN1 (1–3). Moreover, regularly updated recommendations for screening and diagnosis are available on the GTE website in order to help physicians to follow the same rules in all of the centers (http://sfendocrino.org/IMG/pdf/livret_NEM1_2006-2.pdf). Nevertheless, despite the apparent clarity of the diagnosis criteria, some uncertainties may remain regarding MEN1 diagnosis in routine practice (24, 25). Such uncertain patients were analyzed carefully using complementary criteria before their inclusion in the database when genetic analyses were negative (18).

Another strength of the study is the multicenter aspect of the data collection and the size of the cohort. All the French regions and some Belgian regions were involved, and our cohort was more than twice as big as the largest previously published cohorts regularly quoted in the literature. These large cohorts comprised more than 200 MEN1 patients. They were located in the USA ($n=233$: 1951–1997 period of MEN1 diagnosis), in Italy ($n=221$: 1990–2003 period of MEN1 diagnosis), in the United Kingdom ($n=220$: unknown

Table 3 Proportion of patients with MEN1 diagnosis at the time of first lesion.

	Males		Females		P*
	n ^a	n (%) ^b	n ^a	n (%) ^b	
Any lesion	310	189 (61.0)	424	225 (53.1)	0.03
As first lesion					
Pancreatic tumor	121	77 (63.6)	116	71 (61.2)	0.70
Hyperparathyroidism	217	160 (73.7)	267	184 (68.9)	0.24
Pituitary tumor	55	37 (67.3)	129	57 (44.2)	0.004
Other tumors ^c	22	15 (68.2)	24	14 (58.3)	0.49

*P value for comparison between genders by χ^2 test or exact Fisher test with 1 ddl for binary variables.

^aTotal number of patients affected by the mentioned lesion among males and females.

^bNumber and percent of patients presenting the mentioned lesion as the first lesion and diagnosed as MEN1 at the same time among males and females.

^cAdrenal tumors, thymic tumors, and bronchial tumors.

Table 4 Time between the first lesion and the MEN1 diagnosis in patients with delayed diagnosis. Values are presented as median delay (years) after first lesion (95% CI).

	Males		Females		P*
	n ^a	Median delay (95% CI)	n ^a	Median delay (95% CI)	
Any lesion	121	2.2 (0.4–9.0)	199	4.0 (1.0–9.2)	0.14
As first lesion					
Pancreatic tumor	44	1.3 (0.3–3.9)	45	3.1 (1.0–6.0)	0.04
Hyperparathyroidism	57	4.6 (0.5–10.3)	83	3.7 (0.4–8.8)	0.62
Pituitary tumor	18	1.7 (0.3–12.0)	72	5.2 (1.1–11.0)	0.22
Other tumors ^b	7	4.6 (0.1–24.5)	10	1.5 (0.8–2.1)	0.33

95% CI, 95% confidence interval. *P value for comparison between genders by Student's *t*-test or Mann–Whitney *U* test.

^aTotal number of patients affected by a given lesion among males and females.

^bAdrenal tumors, thymic tumors, and bronchial tumors.

period of MEN1 diagnosis), and in Germany ($n=306$: 1980–2006 period of MEN1 diagnosis) (9, 12, 26, 27). The multicenter aspect of this study reduces the risk of bias encountered in single-center cohorts, which may select patients through a specific aspect of the disease such as the age of the patient, or the organ involved (duodeno-pancreas, pituitary, parathyroid glands, etc.). Nevertheless, it is clear that this cohort was heterogeneous: i) the prospective method of GTE data collection dates back to 1991, ii) the work-up and follow-up modalities have changed over the whole study period, iii) the rules in MEN1 patient management may have varied from one center to another despite recommendations, iv) CT, MRI and EUS were only progressively available over the study period, v) and last but not the least, patients did not always comply with medical supervision. Moreover, and as mentioned in the population section, the prevalence of pancreatic lesions was greater at the beginning of the registration process. We know that, before 1981, 80% of the MEN1 patients were first diagnosed with the disease because of ZES/gastrinomas since MEN1 patients were mostly diagnosed through symptomatic presentations and because precise guidelines had not yet been established for the diagnosis of MEN1 (28). These first patients may have over-expressed the importance of duodeno-pancreatic lesions. Nevertheless, only 14% of the patients were diagnosed with MEN1 before 1981, and finally, no major differences in terms of prevalence were found when the GTE results were compared with those of the German MEN1 cohort (29): 93 vs 89% for pHPT, 57 vs 54% for duodeno-pancreatic tumors, and 40 vs 45% for pituitary tumors. These two large and independent cohorts are very similar and are probably representative of MEN1 disease in Western Europe during the past 30 years.

Only scarce and somewhat discordant data are available regarding the prevalence of MEN1 disease and MEN1 lesions by gender. A previous study of 110

patients dating back to 1991 reported that the prevalence of MEN1 and the three most common tumors (pituitary, parathyroid, and duodeno-pancreas) in patients below 55 years was higher in women than in men (11). The study suggested that women were probably more likely to seek a medical consultation. Although this interpretation was obviously not proved, the authors considered that this gender difference was due to a clinical bias. Recently, an overall female predominance was also observed in four MEN1 studies from the United States ($n=233$), from the United Kingdom ($n=220$), from Germany ($n=301$), and from Finland ($n=82$), showing proportions of women of 54, 57, 59, and 57%, thus very close to our figures of 58% (12, 26, 27, 30). The 2007 study from Finland was particularly interesting because the cohort was constituted during a comparable period of time (1982–2001) and was exclusively made of patients with ascertained MEN1 mutations. Nevertheless, the aspect of gender differences was not discussed in these publications. In order to better understand the higher frequency of MEN1 among females, a thorough examination of the characteristics of the most common lesions by gender was necessary. We found a male predominance in the prevalence of duodeno-pancreatic tumors mainly due to ZES-gastrinomas. It is known that pHPT is frequently associated with ZES and that pHPT increases basal acid secretion (31). However, pHPT is not the explanation for this gender difference because pHPT was found as frequently in males as in females. A previous pooled analysis of 16 worldwide studies, including 1009 MEN1 patients with ZES, also found that the proportion of males was 53.8%, thus very close to our value of 52% (16). This male predominance should be compared with the high percentages of men (ranging from 59.5 to 70.1%) reported in studies totally or mostly composed of patients with sporadic ZES, i.e. without an MEN1 background. Our study also confirmed, as already published by the GTE group from a previous smaller cohort, the higher prevalence of pituitary tumors in female MEN1 patients (17). The present analysis underscores the fact that this difference held true for prolactinomas and for other pituitary tumors. Like the high incidence of ZES/gastrinoma in male patients, the high prevalence of pituitary tumors among MEN1 women is in line with the higher female prevalence of pituitary tumors observed in non-MEN1 patients (32, 33). A community-based study recently conducted in the Oxford area among mostly non-MEN1 patients also found a majority of women with pituitary tumors (66.7 vs 67.7% in the present study) (34). Another original finding of this study is the analysis of the gender effect on the probability of MEN1 lesions occurring during a person's lifetime. To our knowledge, only one study was able to estimate the probabilities of tumor occurrence by site, and none by gender (29). We showed that the expression of all MEN1 lesions progressively increases during the lifetime. When

considering gender, the cumulative probability of a pituitary tumor occurring was higher in women than in men at all ages. On the contrary, the cumulative probability of duodeno-pancreatic tumors or thymic tumors occurring was higher in men than in women at all ages. As reported in Fig. 1, the absolute risk for ZES/gastrinoma increases much more in men than in women during their lifetime. We can only hypothesize about the underlying reasons for these gender differences. In sporadic pituitary tumors, somatic MEN1 gene mutations do not significantly contribute to tumorigenesis (35, 36). In about 50% of sporadic ZES/gastrinomas, a mutation in the MEN1 is detected (37–39). Apparently, mutations in other genes may also cause such tumors. In addition, gender apparently influences the risk of tumor development in a different way. Similar molecular events may be involved in sporadic and familial prolactinoma and gastrinoma. If an MEN1 mutation is present, the risk of initiating development of these tumors is very high. In order to explain the difference in disease expression among MEN1 family members, one may assume that other genes as well as gender are involved. Identification of the underlying molecular pathway of tumorigenesis may explain the difference in disease expression, both between family members and between sexes. In sporadic tumors, a different primary mutation may be responsible for tumorigenesis. However, the subsequent steps, including gender, may be similar or even identical to the 'MEN1 pathway' and the same cellular events may be involved in the tumorigenesis. In this regard, it is interesting to remember that menin, the protein encoded by the *MEN1* gene, can act as a co-activator or co-repressor of nuclear hormone receptors including estrogen (ER α) and androgen (AR) receptors (40). As these receptors function as transcription factors, menin can influence patterns of gene expression. Considering the gender-specific differences in concentrations of the hormones involved, and the tissue-specific distribution of their receptors, it should at least be hypothesized that imbalances in ER α or AR activation, as caused by a defect in the *MEN1* gene, may also be involved in sporadic MEN1-associated tumors caused by somatic defects in other genes. This imbalance may thus contribute to the observed gender-specific differences in the prevalence of pituitary tumors and gastrinoma, both among MEN1 patients and in the general population.

An exploratory analysis also revealed for the first time gender differences in the timing of MEN1 diagnosis. In women, MEN1 was less frequently diagnosed at the time of the first lesion, especially when pituitary tumor was the first lesion (MEN1 diagnosed in 44.2% of women versus 67.3% of men). This finding was mainly explained by the smaller number of initial lesions in women. The high prevalence of sporadic pituitary adenomas in females within the general population probably prevents clinicians from diagnosing MEN1 in female patients. Moreover, the clinical presentation of

MEN1 revealed by a pituitary tumor is not specific in terms of secretion and does not help physicians to recognize MEN1 (17). Interestingly, when the first lesions affected other organs such as the duodeno-pancreas or parathyroid, the diagnosis of MEN1 was established similarly in both genders. In patients for whom an immediate diagnosis of MEN1 could not be made on the occurrence of first lesion, no significant difference was found between males and females in the diagnosis time lag, possibly because of low statistical power. Nevertheless, once again, a trend toward a delayed diagnosis in females was found. This tendency was significant in patients in whom the first lesion was a duodeno-pancreatic tumor. As these exploratory findings could have been due to chance, they were interpreted with caution. A delayed diagnosis may be due to a delay in phenotypic expression or to lesser suspicion of the disease in women than in men. This needs to be verified in further studies. As expected with this genetic disease, both a young age at the time of the first lesion and a family history were helpful in increasing the probability of immediate MEN1 diagnosis. Curiously, a family history suggestive of MEN1 at the time of the first lesion was less frequently encountered in women than in men, while positive genetic testing was similar in both genders. Once more, these data suggest that MEN1 disease is less often suspected in women, resulting in an incomplete initial familial inquiry at the time of the first lesion.

For the first time, a comprehensive multicenter study has shown the importance of gender in the phenotype expression of various lesions in MEN1 disease. Possible selection biases exist but are reduced because of the multicenter aspect of the data collection and because of the size of the cohort. Moreover, these results are in agreement with data obtained in the tables available from international publications as regards the MEN1 sex ratio, the sex ratio of pituitary tumors, and ZES/gastrinomas in MEN1 and non-MEN1 patients. This study also emphasizes the difficulties in routine practice with regard to considering pituitary adenomas as MEN1 lesions in women. In order to improve the diagnosis of MEN1 in the future, the following advice may be proposed: i) question patients (male or female) presenting with a pituitary tumor, pHPT, or an endocrine duodeno-pancreatic tumor closely about a family history that evokes MEN1. ii) Test any patient with a pituitary tumor or an endocrine duodeno-pancreatic tumor for hypercalcemia to look for HPT. iii) Carefully screen every patient presenting with a pituitary tumor, pHPT, or endocrine duodeno-pancreatic tumor occurring before 20 years of age for MEN1.

Finally, analysis of gender differences among MEN1 patients showed that phenotype expression is different among males and females and suggests that in female patients the possibility of MEN1 is not sufficiently taken into account.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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