Pituitary adenoma in patients with multiple endocrine neoplasia type 1: a cohort study

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Abstract

Objective: Pituitary adenoma (PA) is one of the three major components of multiple endocrine neoplasia type 1 (MEN1). Recent studies have suggested that MEN1-associated PAs are less aggressive than initially estimated. We propose an analysis of the outcome of PAs with a standard of care treatment in a nationwide cohort of MEN1 patients.
Design: Retrospective observational nationwide cohort study using the MEN1 patient registry from the French Group of Endocrine Tumours (GTE).
Methods: The GTE database population consists of 1435 patients with MEN1. This analysis focused on 551 patients recruited after 2000 with at least 3 years of follow-up. The study outcome was tumour progression of PA defined by an increase in Hardy classification (HC) during follow-up according to referring physician regular reports.
Results: Among 551 MEN1 patients (index and related), 202 (36.7%) had PA, with 114 (56.4%) diagnosed by MEN1-related screening. PAs were defined according to HC as microadenoma (grade I) in 117 cases (57.9%), macroadenoma in 59 (29.2%) with 20 HC grade II and 39 HC grades III–IV and unspecified in 26 (12.8%). They were prolactinomas in 92 cases (45.5%) and non-secreting in 73 (36.1%). After a median follow-up of 3 years among the 137 patients with HC grades I–II, 4 patients (2.9%) presented tumour progression.

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Conclusion: PAs in patients with MEN1 are less aggressive than previously thought. Tumour progression is rare with a standard of care monitoring and treatment, especially in related patients who mostly present non-secreting microadenoma. MRI monitoring for asymptomatic MEN1 patients should be reduced accordingly.

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Introduction

Multiple endocrine neoplasia type 1 (MEN1) is a rare disease that combines several neoplastic conditions mostly represented by parathyroid, pancreatic islet and pituitary tumours. Pituitary tumours, mostly corresponding to pituitary adenomas (PAs), are one of the three major diseases of MEN1. Their incidence varies between 10 and 60% (1) with up to 65% in autopsy series, suggesting that pituitary involvement is under-diagnosed (2). The median age on diagnosis is 40 years, but clinical presentations have been described as early as 5 years of age (3, 4). It has been previously described that PAs in patients with MEN1 were more aggressive than sporadic PAs with increased tumour size and invasiveness as well as a poorer response to treatment (5, 6). The prognosis of PAs is determined by the tumour syndrome (risk of visual impairment), the secretory syndrome (hormonal hypersecretion of prolactin, ACTH or GH) and treatment side effects (surgical complications in particular).

The diagnosis of sporadic PAs has evolved over the last decades owing to wide access to pituitary MRI. Improvement in imaging sensitivity has increased the number of detected pituitary abnormalities – providing updated recommendations regarding pituitary incidentaloma management for the general population (7). Due to the potential aggressiveness of PAs, pituitary monitoring is closer in patients with MEN1. The Clinical Practice Guidelines for MEN1 published in 2012 (8) propose screening for related subjects from age 5 in order to start early clinical, biological and morphological monitoring. The first pituitary MRI should be performed from age 5 and no later than age 10 (9). Biochemical screening which includes an annual assessment of plasma prolactin and IGF-I levels as well as pituitary MRI every 3 years in subjects without PA is recommended (8). There are no specific recommendations for MRI monitoring of MEN1 patients with PA.

In this context, a recent study conducted after the introduction of MEN1-related screening reported a high proportion of non-secreting microadenomas in subjects with MEN1 (10). In that study, tumour progression was rare and slow, thereby challenging the concept that PAs are more aggressive in patients with MEN1. The aim of our study was therefore to update the epidemiological data of the French NEM-1 registry focusing on PAs with recent management, that is, the implementation of family screening in the modern era with MRI and evaluation of the secretory and tumour risk in routine care.

Patients and methods

Study population and data collection

The study population was extracted from the database of 1435 patients from the MEN1-Groupe d'étude des Tumeurs Endocrines (GTE) database as of 2 April 2019. This database collects the results of all patients whose genetic diagnosis was performed in one of the four French laboratories accredited for MEN1 genetic screening (Lille, Lyon, Marseille, Paris). MEN1 was defined according to the clinical practice guidelines for MEN1 (8). The diagnosis of MEN1 was assessed in patients presenting at least two out of three major MEN1 lesions (primary hyperparathyroidism, enteropancreatic neuroendocrine tumours or PA), including both those with and without germline mutations. Diagnosis of MEN1 was also assessed in patients with or without lesion, sharing MEN1 germline mutations identified after the familial screening. Some NEM1 index patients were tested due to suspicious or atypical MEN1, which included individuals with pituitary macroadenoma alone occurring before the age of 30 (11).

For the current analysis, we chose to limit the study to patients who had a diagnosis of MEN1 performed between 1 January 2000 and 31 December 2015. PA diagnosis was established at the last available examination. We excluded patients diagnosed before 2000 in order to homogenise our study population. We stopped our inclusion after 2015 in order to obtain a minimum follow-up of 3 years as of 1 February 2019. The flow chart (Fig. 1) details the steps of

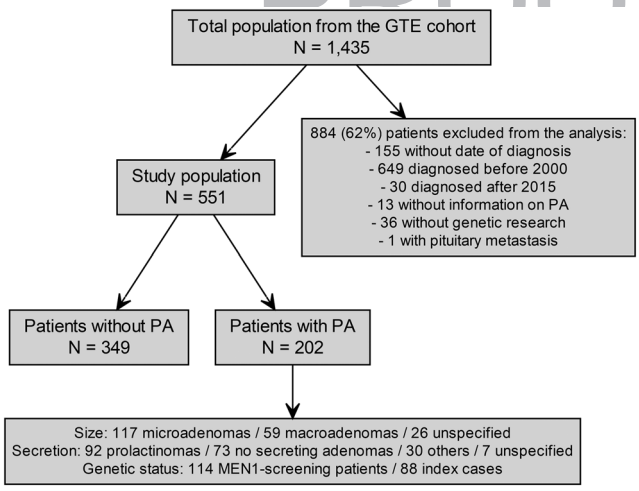

Figure 1

Flowchart. GTE, Groupe d'étude des Tumeurs Endocrines; PA, pituitary adenoma.

patient selection. The final study population corresponds to 551 patients with MEN1 diagnosed between 2000 and 2015.

The clinical data were collected by each patient's referring physician and centralised. The study was sponsored by the University of Burgundy (Dijon), designed in accordance with the Declaration of Helsinki and approved by regulatory authorities: the Commission Nationale Informatique et Liberté – CNIL (reference methodology MR-003).

Diagnosis of pituitary adenoma and other endocrine neoplasms

The diagnosis of PA was reported on the referring physician's statement. Each pituitary lesion was recorded with additional data: age on diagnosis, index case or diagnosis on family screening, presence of clinical signs, presence of hypersecretion, tumour syndrome, MRI imaging results, indication for treatment, follow-up and survival.

We defined other manifestations of MEN1, diagnosed by the referring physician, as follows:

- primary hyperparathyroidism,
- duodeno-pancreatic neuroendocrine tumour,
- other neuroendocrine tumours (NET) including adrenocortical tumours, gastric neuroendocrine tumours and/or carcinoid tumours (thymic NET and lung NET).

Study outcome

Our primary objective was to describe the natural history of PAs owing to the potentially aggressive profile of PAs in MEN1. According to initial imaging, PAs were classified according to Hardy's classification (HC) (12):

- Grade I: microadenomas (<10 mm),
- Grades II: enclosed macroadenomas (≥ 10 mm),
- Grades III and IV (respectively localised and diffuse invasion) grouped under the term invasive macroadenomas.

Statistical analysis

Quantitative data are expressed as mean (±S.D.) or median (25th–75th percentile) in case of skewed distribution. Group comparisons were performed using the Student's *t*-test or Mann–Whitney test for unpaired series, respectively. Categorical data are expressed in numbers (%), and between-group comparisons were performed using Fisher's exact test. The penetrance curves represent the cumulative risk of a diagnosis of MEN1 with a pituitary adenoma, according to age, separately in the index-case population and the related-case population. All statistical analyses were performed using Statistical software R, including survival package. A P-value < 0.05 was considered significant.

Results

General characteristics and diagnosis of PA

Among a study population of 551 patients with MEN1, we found a female predominance (313/551, 56.8%). PA was observed in 202 patients (36.6%) and was the third most common endocrine lesion after primary hyperparathyroidism (480 patients, 87.1%) and pancreatic neuroendocrine tumours (375 subjects, 68.0%). Three patients had multiple PAs (1.5%). The different clinical manifestations of MEN1 and their combinations are schematically presented in Fig. 2. Only one of 551 patients did not present impairment related to MEN1 despite positive genetic testing and is therefore not included in Fig. 2.

The median age on the diagnosis of PA was 32.0 years (22.5–46.0). Among the 88 index patients, PA was the initial manifestation of MEN1 in 65 cases (11.8% of all MEN1 patients). Nine of these 88 patients had no other endocrine lesion. Mirrored, among the 114 screening-related patients,

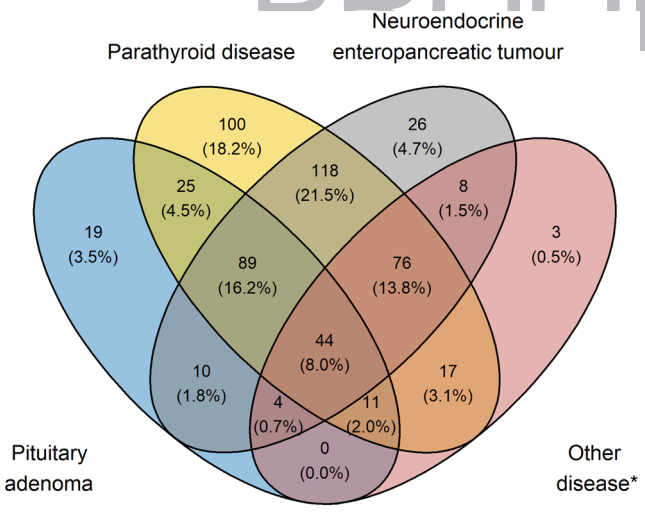

Figure 2

Distribution of MEN1 manifestations and their combinations. Venn diagram representing distribution of MEN1 manifestations in the study population (MEN1 population: 551 patients; with pituitary adenoma: 202 (37%); with parathyroid disease: 480 (87.1%); with neuroendocrine enteropancreatic tumour: 375 (68%); *with other disease: 163 (30%)). *Other disease: adrenocortical tumours and/or gastric neuroendocrine tumours and/or carcinoid tumours (include thymic NET and lung NET). NET, neuroendocrine tumour. Only 1 of 551 patients had no impairment related to MEN1 despite positive genetic testing and is therefore not shown in the figure.

PA was diagnosed during the first assessment in 62 cases. A total of 122 patients had at least one secreting PA (60.3%) and 73 patients (36.1%) had a non-secreting PA. The secreting character was not specified for 7 patients. The baseline clinical characteristics of the patients with MEN1 according to the presence or absence of PA are shown in Table 1. There were no statistically significant differences in terms of primary hyperparathyroidism or duodeno-pancreatic NET frequency in patients with or without PA.

Among the 202 patients with PA, Hardy classification (HC) of the pituitary tumour was available in 176 patients and was not specified for 26 patients. Microadenomas were more frequently observed (117/176, 66.5%) compared with macroadenoma (59/176, 33.5%). The clinical characteristics of MEN1 according to HC are detailed in Table 2. Briefly, index cases were more represented in patients with macroadenoma (57.6%) than in patients with microadenoma (34.2%).

The secretory profile was ascertained in all but not in seven patients and was different when micro- and macro-

Table 1 Characteristics of study participants according to the presence or absence of pituitary adenoma. Quantitative data are expressed using mean ± S.D. Categorical data are expressed in *n* (%). *P*-values are calculated using the Student's *t*-test or Mann–Whitney test for unpaired series, or Fisher's exact test, when appropriate.

	Patients with PA (*n* = 202)	**Patients without PA** (*n* = 349)	***P*-value**
Female (%)	123 (60.9)	190 (54.4)	0.154
Age on diagnosis for MEN1 (years)	36.2 ± 16.3	40.4 ± 16.8	0.005
Index case (yes, %)	88 (43.6)	126 (36.1)	0.086
Genetic test – positive (%)	187 (92.6)	340 (97.4)	0.009
Hyperparathyroidism (%)	169 (83.7)	311 (89.1)	0.086
Pancreatic and duodenal tumour (%)	147 (72.8)	228 (65.3)	0.071
Adrenocortical tumours (%)	45 (22.3)	77 (22.1)	1.000
Gastric neuroendocrine tumours (%)	4 (2.0)	4 (1.1)	0.472
Carcinoid tumours* (%)	17 (8.4)	36 (10.3)	0.549
Follow-up time (years)	5.0 ± 4.4		

*Includes thymic NET and lung NET.
NET, neuroendocrine tumour; PA, pituitary adenoma.

PAs were compared. Microadenomas were mostly non-secreting (53.8%) or microprolactinomas (35.0%). In contrast, macroadenomas were mostly functional with mainly macroprolactinomas (50.8%) and GH-secreting PA (16.9%). Macroadenomas could have multiple secretions (10.2%) whereas this was not observed for microadenomas.

Ninety-seven patients received at least 1 treatment with 31 patients undergoing surgery and 7, all with macroadenoma, received radiotherapy. As expected, treatment was more frequent in patients with macroadenoma (80.7%) compared with those with microadenoma (32.7%). As for the treatment time course, 44 patients were treated immediately or within 1 year of diagnosis. Twelve patients (5.9%) died during follow-up, but no death was related to their PA.

As shown in Table 3, the vast majority of secreting PA were prolactinomas (92/202, 45.5%) of which 30 (32.6%) were macroadenomas. Treatment was initiated immediately or within 1 year of diagnosis in 33 patients with prolactinoma (38.4%) and 65 patients (75.6%) had at least 1 medical treatment. Eight patients (9.3%) underwent surgery, and three patients (3.5%) underwent radiotherapy. The combinations of the treatments for prolactinomas are schematically presented in Supplementary Fig. 1 (see section on supplementary materials given at the end of this article).

Table 2 Characteristics of MEN1 patients with PA according to PA size. Quantitative data are expressed as mean ± S.D. or median (25th–75th percentile), in case of skewed distribution. Categorical data are expressed as *n* (%). *P*-values are calculated using the Student's *t*-test or Mann–Whitney test for unpaired series, or Fisher's exact test, when appropriate. The status of micro/macro PA could not be ascertained in 26 participants. The secretion profile could not be ascertained in 7 participants.

	Entire population (*n* = 202)	Patients with PA		*P*-value
		Microadenoma (*n* = 117)	Macroadenoma (*n* = 59)	
Clinical characteristics				
Female (%)	123 (60.9)	68 (58.1)	35 (59.3)	1.000
Age of diagnosis for MEN1 (years)	36.2 ± 16.3	34.6 ± 15.4	37.2 ± 18.3	0.321
Age at onset of pituitary adenoma (years)	32.0 (22.5–46.0)	32.0 (24.8–44.9)	28.6 (18.9–49.1)	0.215
Min-max	7–82	12–80	7–82	
Index case (%)	88 (43.6)	40 (34.2)	34 (57.6)	0.004
Hardy's classification at baseline (%)				
I: microadenoma	117 (57.9)	117 (100.0)	0	–
II: localised macroadenoma	20 (9.9)	0	20 (33.9)	–
III and IV: invasive tumour	39 (19.3)	0	39 (66.1)	–
Worsening of Hardy classification* (%)	4/137 (2.9)	2/117 (1.7)	2/20 (10)	0.102
Hormonal secretion (%)				
Non-secreting adenoma	73 (36.1)	63 (53.8)	9 (15.3)	<0.001
Prolactinoma	92 (45.5)	41 (35.0)	30 (50.8)	0.449
GH adenoma	12 (5.9)	1 (0.9)	10 (16.9)	<0.001
ACTH adenoma	7 (3.5)	7 (6.0)	0	0.016
TSH adenoma	2 (1.0)	1 (0.9)	1 (1.7)	1.000
Co-secreting adenoma	9 (4.5)	0	6 (10.2)	0.001
Follow-up				
Follow-up duration (years)	4.0 (1.0–8.0)	3.0 (0.0–6.0)	6.0 (4.0–11.0)	<0.001
Number of consultations	3.0 (2.0–6.0)	2.0 (1.0–4.0)	6.0 (4.0–8.0)	<0.001
Frequency of consultations (per year)	1.0 ± 0.6	1.0 ± 0.5	1.1 ± 0.7	0.318
Mean number of brain imaging (per year)	0.6 ± 0.4	0.7 ± 0.4	0.6 ± 0.3	0.150
Treatment				
No treatment (%)	93 (46.0)	83 (70.9)	4 (6.8%)	<0.001
Treatment onset at baseline or during the first year of follow-up (%)	44 (24.4)	13 (13.3)	27 (47.4%)	<0.001
Medical treatment (%)	97 (53.9)	32 (32.7%)	46 (80.7%)	<0.001
Time before onset of medical treatment (years)**	2.0 (1.0–5.5)	2.0 (0.8–4.0)	1.0 (0.0–4.8)	0.315
Surgery (%)	31 (17.2)	8 (8.2)	21 (36.8)	<0.001
Time before first surgery (years)	1.0 (0.0–1.0)	1.0 (0.8–2.0)	1.0 (0.0–1.0)	0.063
Radiotherapy (%)	7 (3.9)	0	7 (12.3)	<0.001
Time before first radiotherapy (years)	1.0 (1.0–2.0)		1.0 (1.0–2.0)	
Death during follow-up (%)	12 (5.9)	6 (5.1)	5 (8.5)	0.509

*HC progression was considered only in those patients with grades I–II, which represents 117 grade I and 20 grade II PA patients; **Time before the onset of medical treatment means the time elapsed since the diagnosis of PA; Medical treatment, surgery and radiotherapy were counted if at least one medical treatment or surgery or radiotherapy was performed during follow-up.
ACTH, adrenocorticotropic hormone; GH, growth hormone; PA, pituitary adenoma; TSH, thyroid-stimulating hormone.

Finally, we compared the clinical characteristics of MEN1 patients with either a pituitary macroadenoma or a secreting microadenoma to those with a non-secreting microadenoma (Table 4). The patients with a non-secreting microadenoma were more frequently relatives diagnosed following a family enquiry. Of note, the death rate during follow-up was similar in both groups: 6.0% in non-secreting microadenoma vs 6.4% secreting microadenoma and macroadenoma, despite a longer follow-up in the latter group (6 vs 3 years).

Table 3 Characteristics of the population according to the secretory profile of PA. Quantitative data are expressed as mean ± s.d. or median (25th–75th percentile), in case of skewed distribution. Categorical data are expressed as *n* (%). The secreting status of PA could not be ascertained in seven participants. Co-secreting adenoma is defined by the secretion of several hormones among prolactinoma, ACTH, GH and TSH.

	Non-secreting adenoma (*n* = 73)	**Prolactinoma** (*n* = 92)	**GH-producing adenoma** (*n* = 12)	**ACTH-producing adenoma** (*n* = 7)	**TSH-producing adenoma** (*n* = 2)	**Co-secreting adenoma** (*n* = 9)
Clinical characteristics						
Female (%)	37 (50.7)	62 (67.4)	9 (75.0)	5 (71.4)	2 (100.0)	4 (44.4)
Age on diagnosis for MEN1 (years)	37.2 ± 16.8	33.0 ± 14.2	44.2 ± 19.2	26.9 ± 5.3	62.3 ± 2.9	41.1 ± 18.2
Age at onset of pituitary adenoma (years)	36.2 (26.9–50.1)	26.3 (20.1–35.5)	49.4 (38.7–58.2)	28.6 (25.5–29.6)	60.2 (59.8–60.7)	33.2 (27.4–39.2)
Min-max	12–80	12–76	7–62	17–35	59–61	16–75
Index case (%)	19 (26.0)	42 (45.7)	9 (75.0)	4 (57.1)	2 (100.0)	8 (88.9)
Hardy's classification at baseline (%)						
I: microadenoma	63 (86.3)	41 (44.6)	1 (8.3)	7 (100.0)	1 (50.0)	0
II: localised macroadenoma	3 (4.1)	8 (8.7)	5 (41.7)	0	1 (50.0)	2 (22.2)
III and IV: invasive tumour	6 (8.2)	22 (23.9)	5 (41.7)	0	0	4 (44.4)
Progression in Hardy's classification*	1/66 (1.5)	2/49 (4.1)	0	0	0	1/2 (50)
Follow-up						
Follow-up duration (years)	3.4 ± 3.8	5.5 ± 4.5	5.5 ± 2.8	5.0 ± 4.5	6.5 ± 1.5	10.8 ± 4.1
Number of consultations	2.0 (1.0–3.0)	4.0 (2.0–7.0)	5.0 (4.0–8.0)	4.5 (2.5–9.5)	3.0 (3.0–3.0)	7.0 (6.0–10.0)
Frequency of consultations (per year)	0.9 ± 0.4	1.0 ± 0.5	1.1 ± 0.3	1.8 ± 1.1	0.5 ± 0.1	0.8 ± 0.4
Number of brain imaging	2.3 ± 1.7	3.0 ± 1.9	3.7 ± 2.0	3.8 ± 2.3	1.0 ± 0.0	4.2 ± 1.9
Mean number of brain imaging (per year)	0.7 ± 0.4	0.5 ± 0.3	0.6 ± 0.3	0.8 ± 0.6	0.1 ± 0.1	0.5 ± 0.3
Treatment						
No treatment (%)	63 (86.3)	24 (26.1)	0	1 (14.3)	0	0
Treatment onset at baseline or during the first year of follow-up (%)	3 (5.0)	33 (38.4)	5 (41.7)	2 (33.3)	0	1 (11.1)
Medical treatment (%)	9 (15.0)	65 (75.6)	7 (58.3)	5 (83.3)	2 (100.0)	8 (88.9)
Time before onset of medical treatment (years)**	8.0 (1.0–11.0)	1.0 (0.5–4.0)	1.0 (0.0–1.5)	2.0 (1.0–2.0)	5.0 (4.5–5.5)	4.0 (2.8–5.2)
Surgery (%)	4 (6.7)	8 (9.3)	8 (66.7)	6 (100.0)	1 (50.0)	3 (33.3)
Time before first surgery (years)	1.0 (0.8–2.5)	0.5 (0.0–3.2)	0.0 (0.0–1.0)	1.0 (1.0–1.8)	0.0 (0.0–0.0)	1.0 (1.0–1.5)
Radiotherapy (%)	1 (1.7)	3 (3.5)	2 (16.7)	0	0	0
Time before first radiotherapy (years)	2.0 (2.0–2.0)	1.0 (1.0–4.5)	1.5 (1.2–1.8)			
Death during follow-up (%)	7 (9.6)	3 (3.3)	1 (8.3)	0	0	0

*HC progression was considered only in those patients with grades I–II; **Time before the onset of medical treatment means the time elapsed since the diagnosis of PA; Medical treatment, surgery and radiotherapy were counted if at least one medical treatment or surgery or radiotherapy was performed during follow-up.

ACTH, adrenocorticotropic hormone; GH, growth hormone; PA, pituitary adenoma; TSH, thyroid-stimulating hormone.

Outcome study with a standard of care treatment

We studied the risk of tumour progression defined by an increase in the HC in patients with HC grades I–II. Out of these 137 patients, only 4 patients (2.9%, 95% CI 0.8–7.3%) had tumour progression (median follow-up 3 years (0–7)). Two microadenomas converted to macroadenomas after 8 and 11 years of follow-up, and two enclosed macroadenomas became invasive after 10 and 8 years of follow-up.

The details of these four patients are presented in Supplementary Table 1. For three patients, a secreting

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Table 4 Non-secreting microadenoma (NSM) vs secreting microadenoma and macroadenoma (SMM) in patients with MEN1. Quantitative data are expressed as mean ± S.D. or median (25th–75th percentile), in case of skewed distribution. Categorical data are expressed as *n* (%). *P*-values are calculated using the Student's *t*-test or Mann–Whitney test for unpaired series, or Fisher's exact test, when appropriate. The status of micro/macro PA could not be ascertained in 26 participants. The secretion profile could not be ascertained in 7 participants.

	Entire population (*n* = 202)	Patients with NSM (*n* = 63)	Patients with SMM (*n* = 113)	*P*-value
Clinical characteristics				
Female (%)	123 (60.9)	33 (52.4)	70 (61.9)	0.264
Age of diagnosis for MEN1 (years)	36.2 ± 16.3	35.7 ± 16.1	35.3 ± 16.7	0.869
Age at onset of pituitary adenoma (years)	35.2 ± 16.4	37.7 ± 16.5	33.8 ± 16.7	0.135
Index case (%)	88 (43.6)	14 (22.2)	60 (53.1)	<0.001
Hardy's classification at baseline (%)				
I: microadenoma	117 (57.9)	63 (100.0)	54 (47.8)	<0.001
II: localised macroadenoma	20 (9.9)	0	20 (17.7)	–
III and IV: invasive tumour	39 (19.3)	0	39 (34.5)	–
Worsening of Hardy classification*	4 (2.2)	1 (2.0)	3 (2.9)	1.000
Hormonal secretion (%)				
Non-secreting adenoma	73 (37.8)	63 (100.0)	9 (8.4)	<0.001
Prolactinoma	92 (47.7)	0	71 (66.4)	–
GH adenoma	12 (6.2)	0	11 (10.3)	–
ACTH adenoma	7 (3.6)	0	7 (6.5)	–
TSH adenoma	2 (1.0)	0	2 (1.9)	–
Co-secreting adenoma	9 (4.5)	0	6 (5.3)	–
Follow-up				
Follow-up duration (years)	4.0 (1.0–8.0)	2.0 (0.0–4.0)	5.0 (2.8–10.0)	<0.001
Number of consultations	3.0 (2.0–6.0)	2.0 (1.0–3.0)	4.0 (2.0–7.0)	<0.001
Frequency of consultations (per year)	1.0 ± 0.6	1.0 ± 0.4	1.1 ± 0.7	0.247
Mean number of brain imaging (per year)	0.6 ± 0.4	0.8 ± 0.4	0.6 ± 0.4	0.002
Treatment				
No treatment (%)	93 (46.0)	61 (96.8)	26 (23.0)	<0.001
Treatment onset at baseline or during the first year of follow-up (%)	44 (24.4)	0	40 (38.5)	<0.001
Medical treatment (%)	97 (53.9)	2 (3.9)	76 (73.1)	<0.001
Time before onset of medical treatment (years)**	2.0 (1.0–5.5)	10.5 (9.2–11.8)	1.0 (0.0–4.0)	0.02
Surgery (%)	31 (17.2)	0	29 (27.9)	<0.001
Time before first surgery (years)	1.5 ± 2.7		1.2 ± 2.3	
Radiotherapy (%)	7 (3.9)	0	7 (6.7)	0.096
Time before first radiotherapy (years)	1.0 (1.0–2.0)		1.0 (1.0–2.0)	
Death during follow-up (%)	12 (5.9)	4 (6.3)	7 (6.2)	1.000

*HC progression was considered only in those patients with grades I–II, which represents 117 grade I and 20 grade II PA patients; **Time before the onset of medical treatment means the time elapsed since the diagnosis of pituitary adenoma; Medical treatment, surgery and radiotherapy were counted if at least one medical treatment or surgery or radiotherapy was performed during follow-up.
ACTH, adrenocorticotropic hormone; GH, growth hormone; TSH, thyroid-stimulating hormone.

adenoma was diagnosed and was successfully treated with medical therapy alone. The patient with non-secreting adenoma was not treated, because tumour growth was only radiological without clinical consequences.

In contrast, 15 patients had tumour reduction defined by a decrease in their HC, including 13 prolactinomas during agonist treatment.

PA in index cases and detected by screening in MEN1-related patients

The age-related penetrance of PA on the entire population of 551 MEN1-patients is shown in Fig. 3. Of note, only 12.2% of the population was diagnosed with PA between 60 and 82 years. When analysing PAs in index-case patients ($n = 88$) and MEN1-related screening patients ($n = 114$) separately, related cases were younger on the diagnosis of PA than index cases (29.0 (19.7–38.2) vs 35.4 (27.0–54.6)),

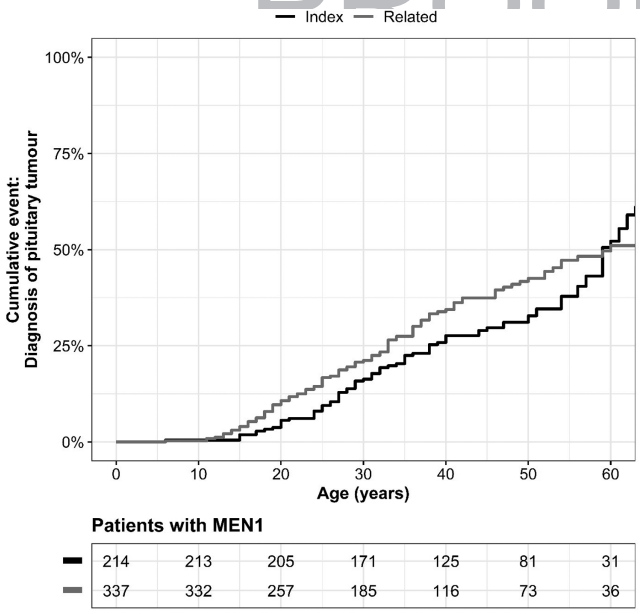

Figure 3

Age-related penetrance of pituitary tumours in patients with MEN1 according to the statute index cases or MEN1-related screening patients (n =551). The black curve shows the age-related penetrance of PA in index patients with MEN1 (events = 88, n = 214) and the grey one in related screening patients with MEN1 (events = 114, n = 337). A threshold of 60 y is applied to this graph because fewer than 20% (precisely 12.2%) of NEM1 patients have a diagnosis of PA after age 60. At age 50, 33% (CI: 26–39%) of index patients had a diagnosis of PA vs 43% (CI: 35–49%) of related patients.

with a predominance of microadenomas on diagnosis (67.5% vs 45.5%). Most of the cases were non-secreting PAs for PA-related patients (54 cases or 47.4%), while prolactinomas were the most frequent in index PA patients (42 cases or 47.8%). This comparative analysis is detailed in Table 5.

Discussion

In this large, multicentre MEN1 registry, the prevalence of PAs was significant (36.6%). The clinical picture of PA in patients with MEN1 has changed since the introduction of systematic pre-symptomatic screening. The majority of PAs diagnosed in MEN1-related patients corresponded to non-secreting microadenomas which did not require any treatment. Microprolactinomas were also common and the most frequently secreting microadenomas. During follow-up, no patient died owing to PA. Among those patients with PA graded as I or II HC, few (4/137; 2.9%) had tumour progression over a median follow-up of 4 years. Tumour progression can therefore be considered slow.

Prevalence and age on the diagnosis of PA were similar to previous cohorts of patients with MEN1. However, significant differences were observed with the French-Belgian cohort study (321 patients, 136 of whom had PA), published in 2002 by our group (5). In this previous report, most PAs were macroadenomas (85% of which 32% were invasive) and most often were prolactinomas. No case of non-secreting microadenoma was reported. This difference is explained by a higher number of index cases with symptomatic presentations, whereas the current cohort is enriched with cases of familial screening of asymptomatic patients. The earlier study found a poorer response to treatment compared with a control group, whereas the risk of tumour progression was low in the present study, probably owing to an initial presentation of least risk for progression and thanks to a now extended therapeutic arsenal in prolactinomas and GH-secreting PAs.

Our results confirmed the more recent data from De Laat *et al.* on 323 Dutch MEN1 patients of whom 123 had pituitary involvement (10). PAs were also mainly non-secreting microadenomas, 91% of which did not require intervention after a median follow-up of 6 years. The frequency of macroadenomas was comparable to our study, respectively 23.0% vs 29.2%. When comparing prolactinomas in both series, only three showed moderate progression in our study while only two showed moderate progression in the Dutch cohort (10).

Improved imaging techniques and their performance could lead to an increasing number of detected pituitary anomalies. This probably explains the increased prevalence of pituitary microadenomas. However, the overall prevalence of PA remains stable. No speculation can be made to explain the discrepancy between historical and more recent populations since the diagnosis situations and imaging tools would make such a comparison spurious and very questionable.

In our database, one patient was excluded because of pituitary metastasis of thymic carcinoma, but no patients presented with pituitary carcinoma. The literature reports three cases of pituitary carcinoma in subjects with MEN1 (13). Caution should therefore be taken, especially in index patients with macroadenoma. It is also important to consider the founder effect. Our results cannot be extrapolated to singular cohorts of patients such as the Terre-Neuve cohort (14), the MEN1-Tasman cohort (15) or even a Brazilian cohort (16).

The clinical implications of our findings must be discussed. Patients with MEN1, particularly those with

Table 5 Characteristics of the population in index cases and MEN1-related screening patients. Quantitative data are expressed as mean ± S.D. or median (25th–75th percentile), in case of skewed distribution. Categorical data are expressed as *n* (%). *P*-values comparing index and relative cases are calculated using the Student's *t*-test or Mann–Whitney test for unpaired series, or Fisher's exact test, when appropriate.

	Index cases (*n* = 88)	**MEN1 screening in relatives** (*n* = 114)	***P*-value**
Clinical characteristics			
Female sex (%)	54 (61.4)	69 (60.5)	1.000
Age on diagnosis for MEN1 (years)	41.5 ± 15.2	32.1 ± 15.9	<0.001
Age at onset of pituitary adenoma (years)	35.4 (27.0–54.6)	29.0 (19.7–38.2)	0.002
Min-max	7–75	7–82	
Hardy's classification at baseline (%)			0.012
I: microadenoma	40 (45.5)	77 (67.5)	–
II: localised macroadenoma	12 (13.6)	8 (7.0)	–
III and IV: invasive tumour	22 (25.0)	17 (14.9)	–
Main involvement (%)			
Hyperparathyroidism	72 (81.8)	97 (85.1)	0.568
Pancreatic and duodenal tumour	65 (73.9)	82 (71.9)	0.749
Adrenocortical tumours	26 (29.5)	19 (16.7)	0.040
Gastric neuroendocrine tumours	4 (4.5)	0	0.034
Carcinoid tumours	7 (8.0)	10 (8.8)	1.000
Hormonal secretion (%)			
Non-secreting adenoma	19 (21.6)	54 (47.4)	<0.001
Prolactinoma	42 (47.8)	50 (43.9)	0.039
GH adenoma	9 (10.2)	3 (2.6)	0.124
ACTH adenoma	4 (4.5)	3 (2.6)	0.716
TSH adenoma	2 (2.3)	0	0.243
Co-secreting adenoma	8 (9.1)	1 (0.9)	0.011
Follow-up			
Follow-up duration (years)	4.5 (1.2–8.0)	4.0 (0.0–8.0)	0.300
Number of consultations	4.0 (2.0–6.0)	3.0 (2.0–7.0)	0.203
Frequency of consultations (per year)	1.1 ± 0.6	1.0 ± 0.5	0.428
Number of brain imaging	3.0 (1.0–4.0)	2.0 (1.0–4.0)	0.090
Mean number of brain imaging (per year)	0.6 ± 0.4	0.6 ± 0.4	0.280
Treatment			
No treatment (%)	29 (33.0)	64 (56.1)	0.169
Treatment onset at baseline or during the first year of follow-up (%)	16 (19.5)	28 (28.6)	0.169
Medical treatment (%)	49 (59.8)	48 (49.0)	0.177
Time before onset of medical treatment (years)*	3.0 (1.0–6.0)	1.0 (0.0–3.8)	0.016
Surgery (%)	21 (25.6)	10 (10.2)	0.009
Time before first surgery (years)	1.0 (0.0–1.0)	1.0 (0.0–1.0)	0.437
Radiotherapy (%)	3 (3.7)	4 (4.1)	1.000
Time before first radiotherapy (years)	2.0 (1.5–5.0)	1.0 (1.0–1.2)	0.162
Death during follow-up (%)	8 (9.1)	4 (3.5)	0.129

*Time before the onset of medical treatment means the time elapsed since the diagnosis of PA; Medical treatment, surgery and radiotherapy were counted if at least one of medical treatment or surgery or radiotherapy was performed during follow-up.
ACTH, adrenocorticotropic hormone; GH, growth hormone; PA, pituitary adenoma; TSH, thyroid-stimulating hormone.

PAs, have a fear of disease that affects their quality of life (17), which is exaggerated since the majority of PAs ultimately prove to be benign and have a slow progression. The distinction between non-secreting microadenoma, which is the most frequent situation and macroadenoma is necessary. It is important to reassure the patient in case of microadenoma since progression was rather low (2/122) and particularly in non-secreting PA, it leads to no endocrine symptoms. However, only a dedicated prospective and standardised study will definitely confirm the need for specific and different monitoring for these two distinct entities (i.e. non-secreting adenoma vs secreting microadenoma and macroadenoma).

In our opinion, it remains important to maintain annual hormone monitoring. In our series, three adenomas were over-secreting at the time of progression in Hardy's classification, suggesting that tumour progression could have been diagnosed by monitoring hormonal secretion

followed by MRI, even in the absence of systematic MRI follow-up. Conversely, the presence of a meningioma (the prevalence of which is higher in MEN1 patients (18, 19)) will necessarily influence the monitoring rate of subsequent brain and pituitary imaging.

Several limitations of our study must be acknowledged. First, recruitment was performed via genetic laboratories that could have missed some patients with MEN1. However, the studied participants were homogenous with a genetic diagnosis. Secondly, the collection of data in the database was not fully standardised with no core centre and was largely based on referring physician assessment. Hormonal assessments were performed locally with different dosage kits, even though this corresponds to a real-life situation, making generalisation easier. Thirdly, PA monitoring was organised solely by the referring physician and no clear recommendations existed to guide this monitoring. The heterogeneity of the data collected may be due to local habits but also to the feedback of information to the database. Our main endpoint, tumour evolution, was analysed in a non-standardised manner. There was no centralised reading of the different MRI images which could certainly have improved our analysis. Anatomopathological data were not accessible via this database. Finally, our primary outcome was rarely encountered, and our statistical power is consequently rather weak. It must be argued that this low number of PA progression reflects the short follow-up, but also our primary hypothesis of a natural history of PAs in MEN1 that was not as aggressive as thought in observational studies before current imaging and therapeutic practices.

Some strengths must also be put forward. To our knowledge, this is the largest cohort of MEN1 patients involved in the prevalence of PAs. This relatively recent series, with follow-up until 2019, allows for the integration of the analysis of modern therapeutic management. This study, carried out after the implementation of the recommendations of systematic family screening for asymptomatic subjects, not only considered index cases but also related subjects.

In conclusion, the present study confirmed that the putative tumour aggressiveness of PAs in MEN1 was not established in current medical handling compared with previously established cohorts prior to the 2000s and it is likely that they behave sporadically. Genetic screening of MEN1 relatives and the systematic implementation of surveillance imaging have altered the known phenotypic profile in subjects with MEN1. While the prevalence of the disease remains largely unchanged, the majority of patients with MEN1 have non-secreting microadenomas which are relatively indolent and do not require intensive MRI surveillance. The personalisation of MRI monitoring is an important question and will require a dedicated prospective trial to further define the clinical management of PAs in MEN1.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EJE-21-0630.

Declaration of interest

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

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Author contribution statement

The list of investigators contributing to the MEN1-GTE registry is provided below: generated data: Annie Costa, Hélène Leclerc. Performed analysis: Olivia Rousseau, Matthieu Wargny. Designed the study and drafted the manuscript: Maëlle Le Bras, Sarra Smati-Grangeon, Bertrand Cariou, Samy Hadjadj. Contributed to the discussion: Pierre Goudet, Thomas Cuny, Frederic Castinetti. Approved the final version of the protocol: all authors. B Cariou and S Hadjadj contributed equally to the work.

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