World J Surg (2010) 34:249–255
DOI 10.1007/s00268-009-0290-1

World Journal of Surgery

Risk Factors and Causes of Death in MEN1 Disease. A GTE (Groupe d'Etude des Tumeurs Endocrines) Cohort Study Among 758 Patients

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Published online: 1 December 2009

Abstract
Background The natural history of multiple endocrine neoplasia type 1 (MEN1) is known through single-institution or single-family studies. We aimed to analyze the risk factors and causes of death in a large cohort of MEN1 patients.
Methods Overall, 758 symptomatic MEN1 patients were identified through the GTE network (Groupe d'étude des Tumeurs Endocrines), which involves French and Belgian genetics laboratories responsible for MEN1 diagnosis and 80 clinical reference centers. The causes of death were analyzed. A frailty model, including time-dependent variables, was used to assess the impact of each clinical lesion, except for hyperparathyroidism, on survival.
Results The median follow-up was 6.3 years. Female gender, family history of MEN1, and recent diagnosis were associated with a lower risk of death. Compared with nonaffected patients, those with thymic tumors (hazard ratio [HR] = 4.64, 95% CI = 1.73-12.41), glucagonomas–vipomas–somatostatinomas (HR = 4.29, 95%

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CI = 1.54-11.93), nonfunctioning pancreatic tumors (HR = 3.43, 95% CI = 1.71-6.88), and gastrinoma (HR = 1.89, 95% CI = 1.09-3.25) had a higher risk of death after adjustment for age, gender, and diagnosis period. The increased risk of death among patients with adrenal tumors was not significant, but three patients died from aggressive adrenal tumors. Pituitary tumors, insulinomas, and bronchial tumors did not increase the risk of death. The proportion of MEN1-related deaths decreased from 76.8 to 71.4% after 1990.

Conclusions The prognosis of MEN1 disease has improved since 1980. Thymic tumors and duodenopancreatic tumors, including nonsecreting pancreatic tumors, increased the risk of death. Rare but aggressive adrenal tumors may also cause death. Most deaths were related to MEN1. New recommendations on abdominal and thoracic imaging are required.

Introduction

Multiple endocrine neoplasia type 1 (MEN1) is an inherited disease predisposing the patient to primary hyperparathyroidism, endocrine enteropancreatic tumors, pituitary adenomas, and adrenal and thymic/bronchial neuroendocrine tumors [1–4]. MEN1 disease may display various clinical associations, and criteria for diagnosis were established in Italy (Gubbio) during a world MEN meeting [5] and are regularly updated [6]. Most cases occur within families, but sporadic cases of MEN1 are now frequently encountered. MEN1 is related to mutations in the *MEN1* gene, an approximately 10-kb gene encoding for menin located on chromosome 11q13 [7–9]. Since 1993, three studies based on selected populations addressed the question of MEN1-related causes of death [10–12]. The work of Wilkinson et al. [10] was based on a single family living in Tasmania. The studies by Doherty et al. [11] and Dean et al. [12] were carried out in the United States and were single-center studies. The aim of this study was to analyze both the causes of death and the relative effect of each lesion on the risk of death in a large French-speaking area. This study was carried out in a large unselected population of 758 MEN1 patients belonging to various families and regularly followed in the multicenter GTE (Groupe d'étude des Tumeurs Endocrines) network [13–19].

Population and methods

The study population was composed of symptomatic MEN1 patients registered in the GTE database. This network, created in February 1991, includes the clinical departments involved in the management of MEN1 patients and the four genetics departments in charge of the diagnosis in France and in Belgium. Data from MEN1 patients diagnosed and followed from 1956 to 1991 in the clinical departments 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 were regularly used to detect new cases. Family trees were established for all index cases and were also used to identify affected family members.

With the help of international guidelines [5, 6], the following inclusion criteria were used: (1) patients with a MEN1 mutation and having at least one of the following lesions: primary hyperparathyroidism (pHPT), pancreatic or duodenal endocrine tumor, pituitary tumor, adrenal tumor, thymic endocrine tumor, bronchial endocrine tumor, and gastric enterochromaffin-like tumor. (2) Patients belonging to an already known MEN1 family in which at least one-first-degree relative was affected and who had at least one of the aforementioned lesions. (3) Patients without positive genetic testing and without familial background with at least two of the three major MEN1 lesions (pHPT, pancreatic or duodenal endocrine tumor, pituitary tumor). The patients who presented only two major lesions were considered with caution since this association may occur randomly in the general population. Other criteria that helped in the diagnosis were used: lesions occurring before the age of 35, pituitary macroadenoma, multiglandular pHPT, pHPT relapsing after surgery, multiple lesions within the pancreas, and the presence of other MEN1-associated endocrine or nonendocrine lesions such as adrenal tumor, thymic neuroendocrine tumor (th-NET), bronchial NET, brain tumor, and MEN1 skin lesions. Patients may or may not have a family history of MEN1 and/or a *MEN1* germline mutation. The full *MEN1* sequence was analyzed as previously described [20]. 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 law. The referent physician provided initial and follow-up data, including clinical features of MEN1 and dates of occurrence, biochemical and imaging tests, and surgical and medical treatments. From copies of the patients' medical files, clinical information was collected on a regular basis and data were included and updated in a computerized file, including 164 items. According to international recommendations [5], patients should be followed up on a regular yearly basis. When data were missing or considered imprecise, an additional query form was sent to the physician in charge

of the patient. Age of onset for a feature was the age at the time of diagnosis for this feature. Overall, 758 symptomatic patients were diagnosed between 1956 and 2005. Follow-up data were available for 721 patients (95.1%).

Statistical analysis

Results for qualitative covariates are expressed as percentages. Pearson's χ^2 test or Fischer's exact test was used when appropriate. In all time-to-event analyses, the baseline date (time zero) was the date of birth. Time to event was defined as the interval between birth and the event of interest (death or occurrence of the MEN1 lesion). Subjects who did not experience the event during their follow-up were censored at their last follow-up or at the study end point, i.e., January 2006. To take intrafamilial correlations into account, a multivariable frailty Cox's proportional hazards model [21] was used to estimate the effect of each clinical lesion on a patient's survival. Studied clinical lesions included the following: pituitary tumors, adrenal tumors, bronchial tumors, th-NET, gastrinomas, insulinomas, nonfunctioning pancreatic tumors (NFPT), and glucagonomas, vipomas, and somatostatinomas (GVS), with the last three tumors grouped together. pHPT was not included in the multivariate analysis because almost all patients had this lesion, which is known to induce only intermittent exposure to hypercalcemia. All the clinical lesions were considered time-dependent covariates in order to avoid a lead time bias and an underestimation of their impact [22]. Estimations of the effect of clinical lesions on the risk of death were adjusted for gender, family history of MEN1, and the period of MEN1 diagnosis (<1980, 1980-1989, 1990-1995, ≥1996), considered fixed-in-time variables. The cutoff chosen for the period of diagnosis corresponded to changes in diagnostic and therapeutic strategies. First-order interactions between fixed-in-time covariates and clinical lesions were systematically checked. For all analyses, $p < 0.05$ 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 analysis.

Results

As shown in Table 1, our cohort included 317 males (41.8%) and 441 females (58.2%). A positive family history was known for 562 patients (74.1%), whereas a genetic mutation was discovered in 504 patients (66.5%). The median time between the date of diagnosis of MEN1 disease and the date of the last follow-up was 6.3 years (interquartile range = 2.2-33 years).

The clinical lesions observed in the 758 symptomatic patients in decreasing frequency were pHPT ($n = 701$, 92.5%), pituitary adenomas ($n = 301$, 39.7%) gastrinomas ($n = 216$, 28.5%), adrenal lesions ($n = 142$, 18.7%), NFPT ($n = 113$, 14.9%), insulinomas ($n = 79$, 10.4%), GVS ($n = 25$, 3.3%), bronchial tumors ($n = 26$, 3.4%), and th-NET ($n = 19$, 2.5%). Overall, pancreatic lesions were observed in 420 patients (55.4%) and represented the second-most frequent type of lesion after pHPT and before pituitary adenomas.

As seen in Table 2, a family history of MEN1, female gender, and a diagnosis of MEN1 after 1980 were all significantly associated with a lower risk of death. Having an insulinoma, a pituitary tumor, or a bronchial tumor at any time during the follow-up had no significant impact on the risk of death. Conversely, patients with at least one pancreatic tumor such as a gastrinoma, a NFPT, or a tumor of the GVS group had an increased risk of death. The risk was multiplied by a factor of 1.9 for patients with a gastrinoma (95% CI = 1.1-3.3), a factor of 3.4 for patients with a NFPT (95% CI = 1.71-6.88), and by a factor of 4.3 for patients with a tumor belonging to the GVS group (95% CI = 1.5-11.9). Patients with a th-NET diagnosed during their follow-up had a risk of death that was almost four times higher than that in patients without this type of lesion (95% CI = 1.7-12.4). The risk of death was also slightly higher in the adrenal lesion group than in nonaffected patients ($p = 0.064$). No significant interaction between clinical lesions and gender, family history of MEN1, or the period of MEN1 diagnosis was observed.

The percentage of MEN1-related deaths decreased from 76.8 to 71.4% after 1990 but this variation was not significant (Table 3). Operative deaths were related mainly to pancreatic surgery (5 of 6 cases). Operative deaths disappeared after 1990. The number of deaths related to ulcerous disease dropped from ten cases before 1990 to one after 1990. Among a total of 23 non-MEN1-related deaths, 11 were due to cancer (9 females, 2 males). Five of the nine females died from breast cancer (55.6%).

Discussion

Despite improvements in diagnosis criteria since Wermer's publication in 1954, the diagnosis of MEN1 remains difficult [1, 6]. The *MEN1* gene was cloned only 11 years ago, and at the moment genetic testing is still negative in up to 10% of MEN1 families [8]. Thus, any clinical study on MEN1 disease requires comprehensive data collection involving many centers and following the same rules in terms of diagnosis and follow-up. The advantage of the GTE network is that it involves referent clinicians from all concerned hospitals throughout France and in some areas

Table 1 Descriptive characteristics of the study population

	All ($N = 758$)		Males ($N = 317$)		Females ($N = 441$)	
	n	(%)	*n*	(%)	*n*	(%)
Lesions						
HPT	701	(92.5)	292	(92.1)	409	(92.7)
Pancreatic tumors	420	(55.4)	190	(59.9)	230	(52.2)
Gastrinoma	216	(28.5)	113	(35.7)	103	(23.4)
Insulinoma	79	(10.4)	28	(8.8)	51	(11.6)
GVS	25	(3.3)	135	(4.1)	12	(2.7)
NSPT	113	(14.9)	43	(13.6)	70	(15.9)
Others	41	(5.41)	19	(5.99)	22	(4.99)
Pituitary tumors	301	(39.7)	96	(30.3)	205	(46.5)
Adrenal tumors	142	(18.7)	61	(19.2)	81	(18.4)
Bronchial tumors	26	(3.4)	12	(3.8)	14	(3.2)
Thymic tumors	19	(2.5)	19	(6.0)	0	(0.0)
Period of NEM1 diagnosis						
<1980	62	(8.2)	27	(8.5)	35	(7.9)
1980-1989	159	(21.0)	61	(19.2)	98	(22.2)
1990-1995	221	(29.2)	93	(29.3)	128	(29.0)
≥1996	314	(41.4)	135	(42.6)	179	(40.6)
Unknown	2	(0.3)	1	(0.3)	1	(0.2)
Age at NEM1 diagnosis						
≤20 years	94	(12.4)	41	(12.9)	53	(12.0)
21-40 years	299	(39.5)	130	(41.0)	169	(38.3)
41-60 years	283	(37.3)	123	(38.8)	160	(36.3)
>60 years	80	(10.6)	22	(6.9)	58	(13.2)
DM	2	(0.3)	1	(0.3)	1	(0.2)
Family history						
Yes	562	(74.1)	253	(79.8)	309	(70.1)
No	190	(25.1)	61	(19.2)	129	(29.3)
Unknown	6	(0.8)	3	(1.0)	3	(0.7)
MEN1 mutation						
Yes	504	(66.5)	225	(71.0)	279	(63.3)
No	95	(12.5)	31	(9.8)	64	(14.5)
Not analyzed	159	(21.0)	61	(19.2)	98	(22.2)

GVS glucagonoma or vipoma or somatostatinoma, *NFPT* nonfunctioning pancreatic tumors, *DM* missing data

of Belgium. Furthermore, all genetic analyses are centralized in the four laboratories involved in the network. The family investigation needed before genetic testing facilitated the registration of all family members and the search for additional clinical information regarding relatives. Follow-up data were available for most of the patients, with a median follow-up duration of 6.3 years. Nevertheless, there were several limitations to the study: one limitation is that the exhaustiveness of patient registration cannot be guaranteed. However, the involvement of all referent centers in the study, as well as the careful attention paid to the identification of family members, suggests that the cohort is probably representative of MEN1 patients. Interestingly, no major clinical differences could be found between this cohort and the 233 MEN1 patients in the Mayo Clinic cohort: There were comparable in age at diagnosis, sex ratio with a slight female predominance, and prevalence of lesions [12]. These findings hold true although the Mayo Clinic study was based on a one-institution experience. Another limitation of the study is related to its long time span with the risk of changes in diagnosis tools and management strategies. Therefore, the multivariate analysis took into account the period of diagnosis in order to define more precisely the impact of each lesion on the risk of death. This adjustment of time was useful since a significant decrease in the risk of death was noted.

The present study confirmed the severity of th-NET and its exclusive development in men, justifying early screening programs. A more comprehensive study on this rare and peculiar lesion has recently been published by the GTE

Table 2 Risk of death according to MEN1 lesion (GTE cohort) using a frailty model

	Hazard ratio	95% CI	*p*
Women versus men	0.46	0.28–0.76	0.003
Familial history of MEN1	0.46	0.27–0.79	0.005
Period of diagnosis			
1980–1989 vs. <1980	0.33	0.18–0.60	<0.001
1990–1995 vs. <1980	0.18	0.09–0.35	<0.001
≥1996 vs. <1980	0.17	0.08–0.40	<0.001
Neuroendocrine thymic tumor	4.64	1.73–12.41	0.002
GVS	4.29	1.54–11.93	0.005
Nonfunctioning pancreatic tumor	3.43	1.71–6.88	0.001
Gastrinoma	1.89	1.09–3.25	0.022
Adrenal tumor	1.72	0.97–3.06	0.064
Bronchial tumor	1.55	0.64–3.77	0.332
Pituitary tumor	1.17	0.72–1.90	0.536
Insulinoma	0.85	0.39–1.86	0.679

GVS glucagonoma or vipoma or somatostatinoma

group using up-to-date information on a series of 21 th-NET patients. The study confirms the bad prognosis of th-NET and the need for yearly imaging workups from age 16 [19].

Regarding pancreatic lesions, this study was the first to assess the impact of the various types of tumors and secretions in terms of survival. Our study stresses the strong impact of NFPT on mortality. NFPT appeared to be as aggressive as gastrinomas or GVS tumors, which were considered the most life-threatening pancreatic lesions thus far [10–12, 16, 23]. In contrast, insulinomas seemed to be less dangerous than other pancreatic tumors. Duodeno-pancreatic islet tumors are known to be the main cause of MEN1 deaths. A recent and comprehensive single-institution study on prognosis and survival of 324 patients with pancreatic endocrine tumor showed that tumor stage (TNM), tumor size, and WHO classification were important in predicting survival [24]. In our study, we considered that assessment of tumor sizes and staging over such a long period of time were not possible since CT scans were only progressively available in the 1980 s and endoscopic ultrasound in the 1990s. The important question of the role of the pancreatic tumor size, whatever the secreting profile, needs to be addressed using a restricted group of patients diagnosed recently and followed by comparable imaging tools. Such a study is being conducted. Nevertheless, except for insulinomas, this study is consistent with that of Akeblad regarding the comparable risk of death between secreting and nonfunctioning pancreatic tumors [24]. Moreover, we conclude that gastrinomas, NFPT, and GVS increase the risk of death with a comparable hazard ratio. The reason for the apparently benign behavior of insulinomas needs to be elucidated; they may be smaller and/or more differentiated [13].

As far as adrenal glands are concerned, a weak but increasing risk of death was noted. Three deaths directly related to adrenal gland lesions were registered. Two cases of adrenocortical carcinoma (ACC) and one case of pheochromocytoma were at a metastatic stage. Another ACC case induced an aggressive Cushing syndrome. These results are consistent with those of Skosgeid et al. [25] and Langer et al. [26] who had already observed that adrenal enlargement may progress to highly aggressive ACC in MEN1 disease. This study thus confirms that MEN1 adrenal tumors have a weak but non-negligible impact on mortality which is due to rare but aggressive tumors.

Hyperparathyroidism was the direct cause of death in only two cases of acute hypercalcemia. Although sporadic pHPT is known to moderately increase mortality [27–29], we did not include hyperparathyroidism in the multivariate analysis. First of all, a large majority of patients were affected by pHPT, rendering the specific impact difficult to study statistically. Second, these patients are intermittently exposed to the risk of hypercalcemia after their diagnosis since they are often operated on and cured, but in many cases relapse occurs. They may be operated on several times. Third, pHPT is not a clear-cut condition. Hypercalcemia arises progressively during MEN1 disease. The impact of pHPT on mortality in MEN1 deserves further study.

The prognosis of MEN1 disease has improved regularly since 1980. The analysis of causes of death showed a slight decline in MEN1-related deaths over time. This was due to the dramatic decrease in operative mortality and the virtual disappearance of deaths related to the complications of ulcerous disease (perforation or hemorrhage). These data may partially explain the decreasing risk of death over time shown in the multivariate analysis. In three previous studies that addressed the question of MEN1 causes of death [10–12], the proportion of deaths directly related to MEN1 ranged from 28 to 46%. This contrasts with our figures of 76.8 and 71.4%, respectively, before and after 1990. Differences in study design and the median follow-up of 6.3 years of the present study may account for this discrepancy. Since most patients still die from MEN1 disease, these results point out the need for further advances in the detection and treatment of life-threatening MEN1 lesions.

As expected, the presence of a family history of MEN1 had a protective effect on the risk of death. Indeed, early detection and follow-up programs set up in already known families may account for this favorable impact. As far as the decreased risk of death in women is concerned, it must be remembered that MEN1 patients are affected by a chronic disease with good survival. Consequently, like in

Table 3 Causes of death

	Diagnosis before 1990	Diagnosis after 1990
Related to MEN1	53 (76.8%)	25 (71.4%)
Due to ulcerous disease (perforation or hemorrhage)	10 (14.5%)	1 (2.8%)
Due to local or metastatic progression	33 (47.8%)	23 (65.7%)
Zollinger–Ellison	12	6
Insulinoma	3	0
Glucagonoma–vipoma–somatostatinoma	2	2
Nonfunctioning pancreatic tumor	5	6
Thymic tumor	2	3
Bronchial tumor	5	0
Gastric tumor	0	1
Pituitary tumor	1	1
Adrenal tumor	2	1
Brain tumor	1	1
Unknown primary tumor	0	2
Other reasons related to	10 (14.5%)	1(2.8%)
Zollinger–Ellison	2 postoperative deaths	1 acute pancreatitis
	1 chemotherapy	
	1 septicemia	
Insulinoma	1 postoperative death	0
	1 hypoglycemia-related suicide	
Glucagonoma–vipoma–somatostatinoma	1 postoperative death	0
Hyperparathyroidism	2 acute hypercalcemias	0
Pituitary tumor	1 postoperative death	0
Unrelated to MEN1	13 (18.8%)	10 (28.6%)
Other cancers	8[a]	3[b]
Other medical causes	5[c]	7[d]
Unknown causes	3 (4.4%)	0 (0%)

[a] Breast (4), tongue (1), bronchus (1), nonendocrine cancer with primary tumor unknown (2)

[b] Breast (1), myeloma (1), kidney (1)

[c] Accident at work (2), hypertension (1), car accident (1), cardiac infarction (1), Alzheimer's disease (1)

[d] Very old age (1), pulmonary embolism (1), cardiac arrhythmia (1), cardiac insufficiency (1), cardiac infarction (2), acute alcoholism (1)

the rest of the population, women with MEN1 have a longer life expectancy than men.

Non-MEN1-related deaths were due to various medical causes but also to other cancers, especially breast cancers. The hypothesis of a link between breast cancer and MEN1 disease has been raised [30]. However, the findings of the present study did not suggest a higher number of breast cancer deaths compared to the general population. Indeed, four deaths from breast cancer would be expected in the GTE cohort according to the national estimation of breast cancer mortality [31].

In conclusion, this study shows that given their high potential for malignancy, their silent course, and their frequency, the detection of NFPT deserves special attention. These lesions require as much attention as other duodenopancreatic lesions such as gastrinomas or GVS [15, 16]. Only a regular imaging work-up may detect them before they turn into aggressive lesions [17, 18]. Current guidelines advocate performing abdominal CT scans or magnetic resonance imaging of MEN1 patients at age 20 and then every 3-5 years [6]. Given our results, imaging every 3 years seems safer. Moreover, the presence of possible malignant adrenal tumors that increase the risk of death confirms this attitude. As far as thymic tumors are concerned, a yearly chest CT is already recommended [6]. Indeed, there are concerns about the radiation dose exposure of yearly chest CT scans on a majority of patients who will not present a thymic tumor. This issue has been addressed by Radiological Societies such as the Fleischner Society [32]. These questions need to be addressed during further expert MEN1 meetings. Improving the detection of these life-threatening lesions may reduce the 71% of MEN1-related deaths in forthcoming years.

Acknowledgments We are grateful to Mr. Philip Bastable for help with translation of the manuscript into English. We also acknowledge the coauthors: C. Ajzenberg, J.J. Altman, F. Archambeaud, J.R. Attali, C. Badet, J. Barbier, M. Barthet, E. Baudin, B. Bauduceau, P. Bernades, X. Bertagna, J. Bertherat, P. Boissel, P. Bouchard, J.M. Boyaval, L. Bresler, J.F. Bretagne, J. Bringer, L. Brunaud, J. Burger, P. Carenco, P. Caron, B. Cathebras, M. Celerier, O. Chabre, G. Chabrier, D. Chadenas, P. Chanson, D. Charitanski, J.A. Chayvialle, C. Colmar Montiel, J.M. Comas, B. Conte Devolx, A. Cortot, E. Cosson, P. Cougard, P. Cubertafond, P. D'Anella, P. Darsy,

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