Multiple endocrine neoplasia type 1 in Northern Finland; clinical features and genotype–phenotype correlation

O Vierimaa¹, T M L Ebeling¹, S Kytölä², R Bloigu³, E Eloranta¹, J Salmi⁴, E Korpi-Hyövälti⁵, L Niskanen⁶, A Orvola⁷, E Elovaara⁸, A Gynther⁹, T Sane¹⁰, M Välimäki¹⁰, J Ignatius, J Leisti and P I Salmela¹

Department of Clinical Genetics, Oulu University Hospital, PB 24, FIN-90029 Oys, Oulu, Finland, ¹Department of Internal Medicine, Oulu University Hospital, FIN-90029 Oys, Oulu, Finland, ²Medix Laboratories Ltd, FIN-02630 Espoo, Finland, ³Department of Medical Informatics, Faculty of Medicine, FIN-90014 Oulu University, Oulu, Finland, ⁴Department of Internal Medicine, Tampere University Hospital, FIN-33014 Tampere, Finland, ⁵Department of Internal Medicine, Seinäjoki Central Hospital, FIN-60220 Seinäjoki, Finland, ⁶Department of Medicine, Kuopio University Hospital, FIN-70211 Kuopio, Finland, ⁷Department of Medicine, Central Hospital of Kanta-Häme, FIN-13530 Hämeenlinna, Finland, ⁸Department of Medicine, Central Hospital of Pohjois-Karjala, FIN-80210 Joensuu, Finland, ⁹Department of Medicine, Central Hospital of Mikkeli, FIN-50100 Mikkeli, Finland and ¹⁰Division of Endocrinology, Department of Medicine, Helsinki University Central Hospital, FIN-00029 Helsinki, Finland

(Correspondence should be addressed to O Vierimaa; Email: outi.vierimaa@oulu.fi)

Abstract

Objective: The existence of genotype–phenotype correlation in multiple endocrine neoplasia type 1 (MEN1) is controversial. Two founder mutations of the *MEN1* gene in Northern Finland gave us an opportunity to compare clinical features among heterozygotes of different mutations.

Design and methods: Study cohort included 82 *MEN1* heterozygotes who were tested for MEN1 during the years 1982–2001. Medical records were reviewed for manifestations of MEN1, other tumours and cause of death by the end of August 2003. Logistic regression analysis was used in evaluating the impact of age, gender and mutational status of affected heterozygotes on the likelihood of developing manifestations of MEN1.

Results: Founder mutations 1466del12 and 1657insC were found in 39 and 29 individuals, and D418N, G156R and R527X mutations in 9, 3 and 2 individuals respectively. Except for pituitary adenoma and nonfunctional pancreatic tumour (NFPT), age was a risk factor for all the disease manifestations. For NFPT, frameshift/nonsense mutations (1657insC, R527X) gave an odds ratio (OR) of 3.26 (95% confidence intervals (CI), 1.27–8.33; $P=0.014$) compared with in-frame/missense mutations (1466del12, D418N, G156R); including the founder mutation carriers ($n=68$) only, the 1657insC mutation gave an OR of 3.56 (CI, 1.29–9.83; $P=0.015$). For gastrinoma, in-frame/missense mutations predicted the risk with an OR of 6.77 (CI, 1.31–35.0; $P=0.022$), and in the founder mutations group the 1466del12 mutation gave an OR of 15.09 (CI, 1.73–131.9, $P=0.014$). **Conclusions:** In this study population, NFPT was more common in the frameshift/nonsense or 1657insC mutation carriers, whereas gastrinoma was more common in the in-frame/missense or 1466del12 mutation carriers.

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Introduction

Multiple endocrine neoplasia type 1 (MEN1, MIM 131100) is an autosomal dominantly inherited syndrome predisposing to parathyroid, neuroendocrine gastroenteropancreatic (GEP) and anterior pituitary tumours. The most frequent manifestation of MEN1 is primary hyperparathyroidism (PHPT) occurring in 82–95% of patients, while enteropancreatic tumours and anterior pituitary adenomas are found in 27–75% and 19–65% respectively (1–6). Adrenal lesions are seen in 5–40% (1, 2, 6, 7) and neuroendocrine tumours of the gastrointestinal tract, bronchus or thymus in 4–9% of patients (1, 2, 6). Leiomyoma of various sites and angiofibroma, collagenoma and lipoma of the skin are also seen in association with MEN1 (8, 9).

The gene for (*MEN1*) was characterised in 1997 (10, 11). *MEN1* is a tumour suppressor gene that encodes a 67 kDa protein of 610 amino acids, named menin, which is found mostly in the nucleus. Menin interacts with several other proteins such as JunD, Smad family members, NF- κ B, vimentin and HSP70, and seems to function as a general regulator of transcription (12–14). Loss of its function through Knudson's two-hit model is an important step that can lead to various tumours seen in this syndrome (15).

To date, about 300 different *MEN1* mutations have been reported (16). They are scattered throughout the entire *MEN1* coding sequence. Most mutations described have been truncating mutations, thus supporting the function of menin as a tumour suppressor. Some mutational hot spots have been

reported several times in the literature (16). Notably, an intron 4 mutation has been encountered in several unrelated families with considerable variation of tumour presentation (17). Some of the recurrent mutations are due to a founder effect, which has been reported, e.g. from Tasmania, Newfoundland and Northern Finland (18–20). In Northern Finland, two different founder mutations (1466del12 and 1657insC) have been found. Both these are located in exon 10 (20). Most reports doubt the existence of any kind of genotype–phenotype correlation in MEN1 syndrome implying that the underlying mutation would not predict the clinical picture. Neither the location of the mutation along the gene nor the mutation type (nonsense, missense, in-frame or frameshift deletion or insertion, splice-site defects) seems to have any effect upon the phenotype (21–24). In previous reports, however, the number of patients carrying the same mutation has usually been small, and this has made phenotype–genotype correlation analysis difficult.

Hitherto, only four studies reporting an apparent founder effect and several affected individuals carrying the same mutation have been reported. The best known of these has been described from Newfoundland and is called the ‘Burin (Newfoundland)’ or prolactinoma variant, where there is an exceptionally high prevalence of prolactinoma and a low prevalence of gastrinoma (19). All 83 patients belonging to 4 different families without a known common ancestor but sharing the same haplotype carried the same R460X (Arg 460Stop) mutation (19). Later, however, this same phenotype has been found to cosegregate even with other mutations (4). In addition, 64 patients from Tasmania carrying the same IVS2-3 (C–G) mutation have been reported (18). The founder effect has also been reported for mutation 512delC (five out of six families originating from the Pennsylvania–Ohio region) and for 416delC (five kindreds also from the USA) (25). Thus, at present, it is unclear whether the prolactinoma variant is due to a genotype–phenotype effect or due to factors not related to the *MEN1* gene.

In Finland, two different founder mutations (1466del12 and 1657insC) have been found (20). Today, more than 100 MEN1 patients with proven mutations are known. A majority of them carry either of the two founder mutations. This enrichment offers a good opportunity to study genotype–phenotype correlations in MEN1. The purpose of our study was to describe the clinical features of Northern Finnish MEN1 patients found during the years 1982–2001 and to evaluate the likelihood of genotype–phenotype correlation among these patients.

Subjects and methods

The study population consists of 82 *MEN1* mutation carriers belonging to 16 families found in the district of Oulu University Hospital during the years 1982–2001.

Initially, 25 index patients received genetic counselling at the Department of Clinical Genetics, Oulu University Hospital, which is responsible for genetic counselling in Northern Finland. Genetic counselling was also offered to their relatives at risk. After genetic counselling, a total of 159 subjects optioned for further studies. Prior to 1997, the ascertainment of heterozygotes was based on both biochemical and radiological information combined later with *MEN1* linkage analysis. All these cases were confirmed by direct mutation analysis when it became possible in 1997. From then onwards all the new cases have been directly analysed by *MEN1* mutation detecting.

Among the 159 individuals studied, the *MEN1* gene analysis revealed 87 heterozygotes including 25 index patients and 62 newly diagnosed family members. Of the 62 newly diagnosed heterozygotes, five were excluded from the analysis for various reasons (Two were tested as newborns, two did not enter the screening programme and one was living outside Finland) and thus the remaining 82 individuals were included in the follow-up study. Altogether 72 subjects appeared to be non-carriers and could be excluded from the follow-ups.

All patients had regular follow-ups at the closest endocrinology unit for screening of the MEN1-related manifestations. The basic follow-up visit every 1 to 3 years consisted of biochemical screening of serum sample (ionized calcium, parathyroid hormone, pancreatic polypeptide (PP), gastrin, chromogranin A (CGA) and prolactin) and radiological imaging (ultrasound/computed tomography/magnetic resonance imaging) of the abdomen, pituitary and parathyroid glands. In cases of active disease, the patients were seen more frequently and a wide range of different diagnostic methods were used, including somatostatin-receptor scintigraphy to detect neuroendocrine tumours at various regions.

The medical records of the *MEN1* heterozygotes were reviewed for the presence and timing of the MEN1-related manifestations, possible other tumours and deaths. The onset and diagnosis of PHPT was defined as the first incidence of hypercalcaemia with an inappropriately elevated serum PTH level. The classification of GEP tumours was based on clinical evidence of excess hormone secretion or lack thereof, and in operated patients was confirmed by histology using the WHO criteria. For nonfunctional pancreatic tumours (NFPT), the diagnosis was based on either constantly elevated tumour markers (S-PP and/or S-CGA) or visualization of the tumours by imaging examinations in the absence of other pancreatic hormone over-secretion and clinical endocrine syndrome. The diagnosis of gastrinoma was based on elevated serum gastrin levels, confirmed in most cases with inappropriate rise during secretin test and/or increased gastric acid output. Pituitary adenomas were also classified according to the presence of hormonal activity or lack thereof on clinical and biochemical bases. They were considered

as microadenomas less than when 10 mm and as macroadenomas when equal to or greater than 10 mm in diameter (26). Adrenal glands were regarded as affected when evidence of hyperplasia or tumours was seen in imaging studies and as hormonally active if so evidenced by biochemical testing of autonomous function in cortisol and aldosterone secretions. In addition to the medical records, the death certificates and the autopsy reports were studied, if available, for evaluating the causes of death.

The follow-up time was counted from the first visit to a health care institution for MEN1 suspicion in the patient or family. The last point of the observation period was counted as the last information concerning MEN1-associated documentation available by the end of August 2003 or patient's death by that time.

SPSS 12.0.1 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Mean ages were reported as mean $\pm$ s.d. Binary logistic regression analysis was used for analysing the covariates affecting the likelihood of having different MEN1 manifestations. The study cohort was analysed in two groups containing either all the ascertained heterozygotes or just the founder mutation carriers. Covariates included in all of the analyses were age at the end of the follow-up, gender and mutational background (mutation class when analysing all the cases, and the exact mutation when analysing the founder mutation carriers). Confidence intervals (CI) of 95% are reported in parenthesis after odds ratio (OR) values. $P < 0.05$ was considered significant. Penetrance of the major manifestations by age was calculated by Kaplan–Meier analysis.

The study has been accepted by the ethical committee of Oulu University Hospital. All patients and their relatives included in this study received genetic counseling and gave an informed consent for DNA studies.

Results

Of the 82 individuals (35 men, 47 women) found to be *MEN1* heterozygous carriers, 68 (83%) were found to carry either the mutation 1466del12 or 1657insC, which are the founder mutations in Northern Finland as described earlier (20). The mutation 1466del12

was found in 39 individuals belonging to 9 families, and 1657insC was found in 29 individuals from 4 families. Three additional mutations D418N, G156R and R527X were found in 9, 3 and 2 individuals, respectively, belonging to 3 different families (Table 1). In-frame/missense mutations (1466del12, D418N, G156R) were carried by 51 individuals and frameshift/nonsense mutations (1657insC, R527X) were carried by 31 individuals.

For the 82 mutation-positive individuals, the mean age at the onset of the follow-up was 40.8 ± 14.6 years (range 11–70 years) and the mean age at the end of the observation period was 48.1 ± 15.4 years (range 18–78 years). The mean duration of the follow-up time was 7.3 ± 4.5 years (range 0–18 years). Prevalence of different MEN1 manifestations in the 82 *MEN1* heterozygotes is shown in Table 2 and age-dependent penetrance of the major manifestations according to Kaplan–Meier analysis in Fig. 1. The results of logistic regression analysis are briefed in Table 3. The major clinical and biochemical manifestations of MEN1 in these mutation-positive individuals were as follows:

PHPT

PHPT was detected in 31 males and 45 females ($n = 76$; 93%) at a mean age of 39.8 ± 13.5 years (range 16–69 years; Table 2). Only six patients (7%) remained normocalcaemic during the follow-up. For these six patients without PHPT, the mean age at the end of the observation period was 33.7 ± 13.6 years (range 18–54 years).

A total of 43 patients (52%) were operated on the parathyroid glands at least once. All of the removed glands showed benign histology except for one patient (patient 4–13), who was found to have metastasized parathyroid carcinoma affecting two glands at the age of 38 years.

In the statistical analysis of the 82 individuals, age appeared to be the only factor that could predict the likelihood of having PHPT, with an OR of 1.08 per year (95% CI, 1.01–1.17; $P = 0.031$). Gender or mutation class did not have any effect. When analysing the carriers of the two founder mutations separately, none

Table 1 Mutations found in the 82 multiple endocrine neoplasia type 1 heterozygotes. For each mutation group the mean age of the heterozygotes at the beginning and at the end of the study is shown.

Mutation	Class and location of mutation	Number (%) of mutation carriers	Mean age $\pm$ s.d. (years)	
			At beginning	At end
1466del12	In-frame, exon 10	39 (48%)	44.6 ± 14.4	51.3 ± 15.3
1657insC	Frameshift, exon 10	29 (35%)	37.7 ± 12.5	45.2 ± 13.8
D418N	Missense, exon 9	9 (11%)	37.9 ± 19.4	45.4 ± 19.4
G156R	Missense, exon 3	3 (4%)	28.9 ± 16.5	37.0 ± 17.8
R527X	Nonsense, exon 10	2 (2%)	41.8 ± 1.9	58.0 ± 2.1

Table 2 Prevalences of the major multiple endocrine neoplasia type 1 (*MEN1*) manifestations among the 82 *MEN1* heterozygotes in relation to the different mutations found.

Tumour	1466del12	1657insC	D418N	G156R	R527X	Total
PHPT	37 (95%)	26 (90%)	8 (89%)	3 (100%)	2 (100%)	76 (93%)
GEP (all)	29 (74%)	21 (72%)	6 (67%)	2 (67%)	2 (100%)	60 (73%)
NFPT	15 (39%)	20 (69%)	4 (44%)	1 (33%)	1 (50%)	41 (50%)
GASTR	15 (39%)	1 (3%)	2 (22%)	—	1 (50%)	19 (23%)
Other	—	1 (3%)	—	1 (33%)	—	2 (2%)
NEGT	2 (5%)	2 (7%)	1 (11%)	—	—	5 (6%)
PIT (all)	10 (26%)	9 (31%)	2 (22%)	2 (67%)	1 (50%)	24 (29%)
PROL	7 (18%)	6 (21%)	2 (22%)	2 (67%)	—	17 (21%)
NFPIT	3 (8%)	2 (7%)	—	—	1 (50%)	6 (7%)
Mixed	—	1 (3%) ^a	—	—	—	1 (1%)
THYM	—	2 (7%)	—	—	1 (50%)	3 (4%)
ADR	15 (39%)	7 (24%)	4 (44%)	1 (33%)	2 (100%)	29 (35%)

PHPT, primary hyperparathyroidism is considered as a sign of parathyroid tumour (hyperplasia or adenoma); GEP, gastroenteropancreatic tumour; NFPT, nonfunctional pancreatic tumour; GASTR, gastrinoma, other GEP, insulinoma (1657insC), growth hormone-releasing-hormone secreting tumour GHRHoma (G156R); NEG, neuroendocrine tumour (carcinoid) of gastrointestinal tract; PIT, pituitary adenoma; PROL, prolactinoma; NFPIT, nonfunctional pituitary adenoma; THYM, neuroendocrine carcinoma of thymus; ADR, adrenal lesions.

^aMixed adenoma in this patient - secreted both prolactin and TSH.

of the covariates (age, gender or mutation) could predict the risk for PHPT.

Neuroendocrine GEP tumours (GEP)

In this patient cohort, four types of GEP tumours could be found; NFPTs, gastrinomas, other hormonally active pancreatic tumours and neuroendocrine tumours of gastrointestinal tract, formerly termed carcinoids. Mean age at the end of the follow-up for the patients not having any signs of GEP tumours was

34.0±12.4 years (range 18–65 years). GEP tumours were found in 26 males and 34 females (*n*=60 or 73%) at a mean age of 46.8±12.8 years (range 21–69 years). Metastasized GEP tumours were present in 13 patients (16%), eight males and five females, at a mean age of 55.1±12.4 years (range 28–70 years). Of the patients with GEP tumours, 18 (30%) had undergone an operation to remove or reduce the size of the tumour. In the statistical analysis of all the 82 subjects, only age at the end of the observation period (OR, 1.12; CI, 1.06–1.19; *P*=0.000) was found to be a risk factor for GEP tumours. Gender or mutation

Figure 1 Cumulative penetrance by Kaplan–Meier analysis of multiple endocrine neoplasia type 1 (*MEN1*), primary hyperparathyroidism (PHPT), gastroenteropancreatic tumour (GEP), gastrinoma (GASTR), nonfunctional pancreatic tumour (NFPT), adrenal lesion (ADR) and pituitary adenoma (PIT) in relation to the age of the 82 *MEN1* mutation carriers.

Table 3 Risk factors for different multiple endocrine neoplasia type 1 (MEN1) manifestations found through logistic regression analysis including age, gender and mutational status as covariates in the group of 82 *MEN1* mutation carriers (top) and in the group of 68 *MEN1* founder mutation carriers (below); OR, odds ratio; CI, confidence intervals of 95%.

Covariate	OR	CI	P
Age			
PHPT	1.08	1.01–1.17	0.031
GEP (all)	1.12	1.06–1.19	0.000
Gastrinoma	1.09	1.04–1.15	0.001
Metastasized GEP	1.07	1.02–1.12	0.008
ADR	1.09	1.05–1.14	0.000
Gender	Not found to be a risk factor		
In-frame deletion/missense mutation			
Gastrinoma	6.77	1.31–35.0	0.022
Frameshift insertion/nonsense mutation			
NFPT	3.26	1.27–8.33	0.014
Age			
GEP (all)	1.11	1.05–1.17	0.000
Gastrinoma	1.08	1.03–1.14	0.004
Metastasized GEP	1.08	1.03–1.15	0.005
ADR	1.09	1.04–1.14	0.000
Gender (male)			
Metastasized GEP	4.27	1.03–17.6	0.045
1466del12 mutation			
Gastrinoma	15.1	1.73–131.9	0.014
1657insC mutation			
NFPT	3.56	1.29–9.83	0.015

PHPT, primary hyperparathyroidism; GEP, gastroenteropancreatic tumour; NFPT, nonfunctional pancreatic tumour, gastrinoma, metastasized GEP, pituitary adenoma, prolactinoma, nonfunctional pituitary adenoma; ADR, adrenal lesions.

status had no effect. The result was similar in the subgroup of the founder mutations carriers, with age being the only significant risk factor (OR, 1.11; CI, 1.05–1.17; $P=0.000$).

The most prevalent type of GEP tumour was a NFPT present in 17 males and 24 females ($n=41$ or 50%) at a mean age of 45.3 ± 12.5 years (range 23–69 years). Of these, 20 (49%) had the 1657insC, 15 (37%) the 1466del12, 4 (10%) the D418N and 1 (2%) the R527X and G156R mutations. The risk for NFPT could not be predicted by age or gender, but the mutation class including the frameshift and nonsense mutations gave an OR of 3.26 (CI, 1.27–8.33; $P=0.014$) compared with the other mutation class with in-frame and missense changes in the group of 82 subjects. Among the two founder mutations, 1657insC appeared to be a risk factor for NFPTs with an OR of 3.56 (CI, 1.29–9.83, $P=0.015$).

Gastrinomas were suspected clinically and biochemically in 8 males and 11 females ($n=19$ or 23%) at a mean age of 51.6 ± 11.4 years (range 34–70 years). Of these patients, 15 (79%) had the 1466del12 founder mutation. Two other patients (11%) had the D418N mutation, one patient (5%) the 1657insC founder mutation and another one (5%) the R527X mutation. Gastrinoma patients were found in seven out of nine (78%) of the families carrying the 1466del12 mutation. For the whole material, risk factors for gastrinoma were age (OR, 1.09; CI, 1.04–1.15; $P=0.001$) and mutation class including in-frame and

missense changes (OR, 6.77; CI, 1.31–35.0; $P=0.022$). In the founder mutations group, the 1466del12 mutation was strongly associated with gastrinoma and gave an OR of 15.1 (CI, 1.73–131.9; $P=0.014$) compared to the 1657insC mutation; age gave an OR of 1.08 (CI, 1.03–1.14; $P=0.004$).

An insulinoma was found in one female patient (age 31 years), and a pancreatic growth hormone-releasing hormone secreting tumour resulting in acromegaly was seen in one male patient (age 21 years). Neuroendocrine tumours of the gastrointestinal tract (other than duodenal gastrinomas) were found in five female patients with a mean age of 55.4 ± 9.9 years (range 44–68 years), associating with hypergastrinemia in three of them. All of these five patients were also affected by pancreatic endocrine lesions.

All the patients with metastasized GEP tumours had either the 1466del12 (nine cases) or the 1657insC (four cases) mutation. Lymph node metastases were found in three males and three females, and liver metastases were found in five males and two females. The risk for metastases was increased by advancing age in both settings (82 vs 68 patients), with an OR of 1.07 (CI, 1.02–1.12, $P=0.008$) and 1.08 (CI, 1.03–1.15, $P=0.005$) respectively. In addition, in the founder mutations group, male gender gave an OR of 4.27 (CI, 1.03–17.6; $P=0.045$).

Pituitary tumours

Pituitary adenomas were found in 24 patients (29%), 7 males, 17 females, at a mean age of 40.2 ± 14.4 years (range 12–62 years). Mean age for those without a tumour was 47.5 ± 16.0 years (range 18–78 years) at the end of the follow-up. Among the patients with pituitary adenomas, 17 (71%) had prolactinoma, 6 (25%) had a nonfunctional tumour and 1 had a mixed adenoma secreting both prolactin and TSH. Upon imaging, 12 (50%) were classified as macroadenomas and 11 (46%) were microadenomas. One prolactinoma could not be visualized. Of the patients with pituitary adenomas, 12 (50%) had received some therapy. Dopamine agonist treatment had been given to 10 (42%), and 5 had also been operated. Another patient with prolactinoma received only operative treatment, and one further patient with a nonfunctional adenoma had received radiation therapy.

In addition to the patients with adenomas, there was one further patient (patient 4–13) with sellar tumour diagnosed at 9 years of age. According to the histology report, the removed tumour was angiosarcoma. The tumour sample was not available for review. The patient received radiation therapy and was followed-up by endocrinologist for panhypopituitarism. At 37 years of age, he was found to be a *MEN1* heterozygote through family screening. Two years after entering the follow-up, he died of metastasized parathyroid cancer.

The risk of pituitary adenoma or prolactinoma was not predicted by age, gender or mutational background in either of the settings.

Other neuroendocrine tumours

Neuroendocrine tumours beyond the gastrointestinal tract were all thymic in origin (thymic carcinoids or neuroendocrine carcinoma of thymus) and were found in three male patients. The patients were two brothers with the 1657insC mutation at ages 45 and 52 years and another male patient with the R527X mutation at 55 years of age. By the end of the follow-up, the brothers had developed local recurrences at 47 and 55 years of age, and the former was also found to have skeletal metastases in the spine before his death (patient 12-8). The third patient did not show any signs of thymic neuroendocrine carcinoma six months after the operation.

Adrenal lesions

Adrenal lesions were present in 29 (35%) of the patients (12 males, 17 females) at a mean age of 53.7 ± 10.6 years (range, 32–70 years). All the lesions were considered benign and hormonally inactive, except for two patients, who had subclinical hypercortisolism. Of the patients with adrenal lesions, 28 (97%) were also affected by one or more GEP tumours including 15 with NFPTs (52%), 12 with gastrinomas (41%) and 1 with both (3%).

Age was the only variable that could predict the likelihood of having adrenal lesions with an OR of 1.09 (CI, 1.05–1.14; $P=0.000$) in the group of all the patients, and similarly 1.09 (CI, 1.04–1.14; $P=0.000$) in the founder mutations group.

Other tumours

Other tumours found in the study population are shown in Table 4. Systematic search for cutaneous tumours or uterine leiomyomas was not performed.

Deaths

During the observation period, nine men and six women died at a mean age of 59.0 ± 12.7 years (range 39–72 years) and 62.9 ± 15.0 years (range 36–79 years) respectively (Table 5). MEN1 was considered to be a direct cause of death in seven cases – a metastasized GEP tumour in five patients and a parathyroid carcinoma in one patient. In addition, for one patient diagnosed with gastrinoma 15 years earlier, the cause of death was haemorrhage from a duodenal ulcer. He had refused to go to the follow-up visits 8 years earlier. MEN1 was a contributing factor of death in three cases, presenting as a metastasized pancreatic neuroendocrine tumour in two patients and as a thymic neuroendocrine

carcinoma in one patient. Five patients died of non-MEN1-related causes (Table 5).

Discussion

Well described in the literature more than 100 years ago (27), MEN1 still appears a challenge for genetic counsellors and clinicians regarding the prognosis, follow-up and clinical manifestations. Molecular diagnostic methods have greatly improved the diagnosis of MEN1, but lack of knowledge about the genotype–phenotype correlation as well as inconsistent opinions regarding the risk of developing various tumours is problematic, especially when doing predictive genetic testing.

Two founder mutations common in Northern Finland and resulting in a cluster of MEN1 patients (20), as well as a well-organized health care system, offer a good opportunity to study this disease with unbiased material on a population basis. In the present study, we found 15 patients (38%) with gastrinoma among 39 individuals carrying the 1466del12 mutation, and only 1 patient (3%) with gastrinoma among 29 individuals carrying the 1657insC mutation. This seems to indicate that the 1466del12 carrier patients are more prone to developing gastrinomas. On the other hand, the prevalence of NFPTs among the 1466del12 mutation carriers was significantly lower, 15 (38%) vs 20 (69%), when compared to 1657insC mutation carriers. Resembling our findings, enteropancreatic lesions showed intrafamilial homogeneity in a 10-year prospective screening study published from Sweden (5). In their study, insulin–proinsulin excess was significantly overrepresented in a family with a pronounced malignant profile of their pancreatic tumours, whereas in another family all pancreatic lesions were benign and only the Zollinger–Ellison syndrome was displayed. Contrary to the study by Skogseid *et al.* (5), we could not find any differences between families according to the malignant behaviour of GEP tumours. Instead, male gender seemed to be a risk factor for developing metastasising GEP tumours.

The 1466del12 mutation, located in exon 10, is an in-frame deletion that is predicted to shorten the menin protein by four amino acids at codons 453–456. The deleted region locates in the area that is required for interaction with PEM and NM23H1 proteins (12). The frameshift mutation 1657insC at codon 516 is predicted to cause a premature stop codon, 14 codons upstream (17). This affects the binding site with Smad3 and cuts the nuclear localization signal-2 off (12). It is not known whether these changes in interaction due to MEN1 mutations have any role in the tumourigenesis of gastrinomas or NFPTs.

Hao *et al.* described two kindreds (A and B) with low prevalence of gastrinoma (10%) and high prevalence of prolactinoma (40%) (4). The authors pointed out that the difference in typical MEN1 was more striking for

Table 4 Other than classical multiple endocrine neoplasia type 1 (MEN 1) tumours among the 82 *MEN1* heterozygotes. Patients 4-3 and 4-4 are sisters. Patients 14-12, 14-14 and 14-28 are siblings, and patient 14-54 is a daughter of one of their sisters. Patient 11-6 is an aunt to patient 11-21.

Patient	Sex	Age at diagnosis (year)	Mutation	Location and type of tumour
1-17	F	34	1466del12	Breast; invasive ductal carcinoma
2-19	F	59	1466del12	Kidney; angiomyolipoma
4-3	F	60, 60, 67	1466del12	Thyroid gland; papillary carcinoma. Kidney; clear cell carcinoma. Breast; invasive ductal carcinoma. Uterus; leiomyoma, leiomyolipoma
4-4	F	39	1466del12	Uterus; mesodermal mixed tumour
6-9	F	61	1466del12	Kidney; angiomyolipoma
6-12	F	62	1466del12	Ileum; leiomyoma
9-103	F	32	1466del12	Ventricle; leiomyoma
9-150	M	64	1466del12	Epididymis; leiomyoma
14-12	F	61	1657insC	Head; meningioma
14-14	M	71	1657insC	Prostate; adenocarcinoma, bladder; transitional cell carcinoma
14-28	F	39, 45	1657insC	Thyroid gland; papillary carcinoma. Head; meningioma
14-54	F	43	1657insC	Thyroid gland; papillary carcinoma
11-6	F	51	D418N	Thyroid gland; medullary carcinoma
11-21	F	27	D418N	Thyroid gland; papillary carcinoma
18-5	M	55	R527X	Kidney; multifocal papillary carcinoma

gastrinoma than for prolactinoma. Patients from kindred B harboured a nonsense mutation Y312X, while no *MEN1* mutation was identified in kindred A. Patients with a prolactinoma variant from Newfoundland had a nonsense mutation R460X. A common finding between cases with a prolactinoma variant and 1657insC mutation carriers is a low prevalence of gastrinoma. Also, all three mutations lead to truncated proteins, like most of the *MEN1* mutations (12). In the present study, the mutation class leading to truncated proteins (frame-shift insertion/nonsense mutation) was found to be a risk factor for NFPT, while mutation class leading to presumably lesser changes in the menin protein (in-frame deletion/missense mutations) predicted a risk for gastrinomas. In a paper on genotype–phenotype

correlation of *MEN1* mutations in sporadic gastrinomas (28), authors combined their data with results taken from other cases of sporadic gastrinomas (29). They stated that 40% (11 out of 28) of mutations described (eight missense and three in-frame deletions) altered the amino acid sequence of menin, while 60% (17 out of 28) resulted in a truncated protein. In familial MEN1, the majority (73%) of the mutations lead to a truncated protein (21–23).

In the present study, the likelihood of having a GEP tumour was increased with advancing age, with an OR of 1.12 in the entire group and 1.11 in the subgroup of the founder mutation carriers. According to Kaplan–Meier analysis, the penetrance of GEP tumours is 100% by 70 years of age (Fig. 1). Similar to the findings in a

Table 5 Cause of death of the 15 multiple endocrine neoplasia type 1 (*MEN1*) heterozygotes who died during the follow-up. Contributing factors of death are shown in parentheses.

Patient	Sex	Age at death (years)	Mutation	Cause of death (*if unrelated to MEN1)
1-3	F	70	1466del12	Pancreatic gastrinoma with liver metastases
1-7	M	70	1466del12	Bleeding duodenal ulcer due to gastrinoma
1-12	M	52	1466del12	Mesenteric artery thrombosis*
1-17	F	36	1466del12	Breast cancer with metastases*
2-19	F	62	1466del12	Cor pulmonale* (nonfunctional pancreatic tumour with local lymph node metastases)
3-31	M	44	1466del12	Suicide*
4-13	M	39	1466del12	Parathyroid carcinoma with multiple metastases
7-4	M	72	1466del12	Pancreatic gastrinoma with liver metastases
9-159	M	59	1466del12	Nonfunctional pancreatic tumour with liver metastases
11-6	F	79	D418N	Acute myocardial infarction* (diabetes)
12-8	M	51	1657insC	Cardiac insufficiency due to chronic pericarditis* (neuroendocrine carcinoma of the thymus)
14-12	F	70	1657insC	Nonfunctional pancreatic tumour with local lymph node metastases
14-14	M	72	1657insC	Pulmonary artery embolism after cholecystectomy for a necrotic cholecystitis*
14-18	M	68	1657insC	Lewy body dementia* (non-functional pancreatic tumour with liver metastases)
14-23	F	57	1657insC	Neuroendocrine carcinoma of the stomach and the duodenum with multiple metastases

Tasmanian kindred study (2), however, when NFPTs were analysed alone they were not associated with advancing age.

Our findings of age-related penetrance of other various MEN1 lesions are in agreement with previous studies (2, 4, 5, 30). In the present study, the peak of the prevalence of pituitary tumours is reached at around 60 years of age (Fig. 1), and age was not found to be a risk factor for pituitary tumours. A similar finding with prolactinoma was also seen in the Tasmanian kindred study (2). Also in our study, mutational background or gender did not predict the risk for pituitary adenoma or prolactinoma. In a large multicentre study, Vergès *et al.* (6) found that 85% of the tumours were macroadenomas, whereas in our study the proportion of macroadenomas was 50%. This difference may reflect the higher proportion of newly diagnosed heterozygotes with early diagnoses in our study. Also, in the study of Vergès *et al.* (6), there were tumours secreting growth hormone (GH) or adrenocorticotrophin in 4 and 2% respectively, and cosecreting and nonsecreting tumours in 4 and 6% respectively. The almost total lack of functioning pituitary adenomas other than prolactinomas in our study may be due to the overall lower number of pituitary tumours as compared with the number of pituitary adenomas ($n=136$) in the large multicentre study (6). Nevertheless, the lack of GH-secreting adenomas has also been shown in the Tasmanian kindred where 124 patients were reviewed (32).

The only identifiable risk factor for developing PHPT was advancing age, with an OR of 1.08 per year. According to Kaplan–Meier analysis, the penetrance of PHPT would be 100% by 70 years of age (Fig. 1). One patient (Table 5, patient 4–13) was found to have multiglandular parathyroid cancer, which is extremely rare either as a sporadic form or associated with MEN1. It is not known whether the past radiation therapy on presumed sellar angiosarcoma or peculiar family history of different cancers (Table 4; patient 4–3 is the mother and 4–4 the mother's sister of patient 4–13) had any aetiological impact on the development of parathyroid cancer.

The prevalence of adrenal tumours (35%) in this study is one of the highest reported in the literature (1, 2, 6, 7). This could be due to the high frequency of imaging studies we used. There are also reports including adrenal carcinoma in a varying amount of patients (7, 33). We could find only benign lesions, and only two were associated with subclinical hypercortisolism. Similarly, indolent courses of adrenal lesions has also been reported elsewhere (32, 35).

The occurrence of neuroendocrine gastrointestinal tumours (known earlier as carcinoids) only in women in the present study may be a coincidence. Nevertheless, in this study we noted thymic neuroendocrine tumours only in men in accordance with the previous reports (36, 37). Although we did not find any bronchial

neuroendocrine tumours in our study, they are usually seen more frequently in women (38). Regarding these data, it is apparent that there exists some clinical variation in MEN1 according to the gender of the affected heterozygote.

There were five cases of thyroid cancer in this study. The aetiology of these and other tumours outside the classical MEN1 tumour spectrum (Table 4) noted in our study is not known. However, others had shown by loss of heterozygosity studies that leiomyomas of the oesophagus and uterus, meningioma and lipoma may be part of MEN1 syndrome (8, 9, 39). It is also of note that medullary thyroid carcinoma (Table 4, patient 11–6) is a typical finding in patients with MEN2 and its occurrence in our patient with MEN1 is probably coincidence.

Of the deaths directly caused by MEN1, six (86%) were caused by metastasized tumours associated with MEN1 and only one was caused by complications of peptic ulcer disease. This is in accordance with some recent studies (30, 40, 41), whereas in older studies peptic ulcer disease was the most common MEN1-associated cause of death (42, 43). Owing to the small overall number of deaths in this study, no further analysis on mortality was undertaken. We have previously shown that *MEN1* gene founder mutations did not cause harmful effect on survival in a historical cohort (44).

In conclusion, our study indicates that there is some variation in the risks for certain types of GEP tumours between patients with different *MEN1* mutations. Whether this phenomenon is caused by mutation *per se* and subsequent variations of mutated menin products in different transcriptional interactions or some other factor, like a modifier gene cosegregating with *MEN1* gene, needs further studying. Also, further study is needed before extending these findings from our northern Finnish families to other families carrying the same *MEN1* gene mutations.

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