Impact of Delay in Diagnosis in Outcomes in MEN1: Results From the Dutch MEN1 Study Group

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Objective: Identifying a germline mutation in the multiple endocrine neoplasia type 1 (MEN1) gene in an index case has consequences for a whole family. Eligible family members should be offered genetic counseling and MEN1 mutation testing. Subsequently, clinical screening of mutation carriers according to the guidelines should be initiated. We assessed whether there is a lag time from MEN1 diagnosis of the index case to MEN1 diagnosis of family members. In addition, we determined whether this lag time was associated with an increased morbidity and mortality risk.

Design: A cohort study was performed using the Dutch MEN1 database, including >90% of the Dutch MEN1 population >16 years of age (n = 393).

Results: Fifty-eight MEN1 families were identified, of whom 57 were index cases and 247 were non-index cases (n = 304). The median lag time in MEN1 diagnosis of family members was 3.5 (range, 0–30) years. At the time of MEN1 diagnosis, 30 (12.1%) non-index cases had a duodenopancreatic neuroendocrine tumor, of whom 20% had metastases with a mean lag time of 10.9 years, in comparison with 7.1 years without metastases. Twenty-five (10.1%) non-index cases had a pituitary tumor, of whom 80% had a microadenoma and 20% had a macroadenoma, with mean lag times of 7.2 and 10.6 years, respectively. Ninety-five (38.4%) non-index cases had a primary hyperparathyroidism with a mean lag time of 9.5 years in comparison with seven patients without a primary hyperparathyroidism with a mean lag time of 3 years ($P = .005$). Ten non-index cases died because of a MEN1-related cause that developed during or before the lag time.

Conclusion: There is a clinically relevant delay in MEN1 diagnosis in families because of a lag time between the diagnosis of an index case and the rest of the family. More emphasis should be placed on the conduct of proper counseling and genetic testing in all eligible family members. (***J Clin Endocrinol Metab*** **101: 1159–1165, 2016)**

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Abbreviations: dpNET, duodenopancreatic NET; MEN1, multiple endocrine neoplasia type 1; NET, neuroendocrine tumor; pHPT, primary hyperparathyroidism; PIT, pituitary tumor.

Multiple endocrine neoplasia type 1 (MEN1) is a rare, genetically inherited disease caused by a germline mutation in chromosome 11q13. It is inherited in an autosomal dominant pattern, and therefore the risk of carriership in first-degree relatives of MEN1 patients is 50%. MEN1 is characterized by the combined occurrence of: 1) parathyroid hyperplasia or adenomas causing primary hyperparathyroidism (pHPT); 2) neuroendocrine tumors (NETs) of the pancreas and duodenum; 3) pituitary tumors (PITs); 4) NET of the stomach, thymus, and lung; and 5) adrenal hyperplasia or adenomas. Mortality is mostly related to thymic NETs and duodenopancreatic NETs (dpNETs) (1). The prevalence of MEN1 is estimated at three to four per 100 000, which underscores the rarity of the disease (2).

The MEN1 diagnosis in an individual is established if one of the following three criteria is met: the presence of two or more primary MEN1-related endocrine tumors (ie, pHPT, dpNET, and PIT); the occurrence of one of the MEN1-associated tumors in a first-degree relative of a patient with a clinical diagnosis of MEN1; and identification of a germline MEN1 mutation (3). In case patients with sporadically occurring tumors are suspected for MEN1, their MEN1 risk can be calculated (4). However, considering the very low prevalence of the disease, a doctor's delay in recognizing MEN1 in patients with apparently sporadically occurring MEN1-related tumors seems obvious. The lag time between index diagnosis and diagnosis of family members could be considered another type of delay.

The consequences of both types of delay in diagnosis can be deleterious. In several MEN1 cohorts, a significantly reduced life expectancy in patients with MEN1 was described in comparison with the age-matched general population. Causes of death were often directly related to MEN1 (4–6). Earlier diagnosis may result in a decrease of premature mortality (4). Periodic screening for mutation carriers has been proposed to reduce morbidity and mortality because manifestations are often discovered in a presymptomatic phase, and treatment can be initiated in time to prevent further progression (3, 7). Genetic screening leads to less morbidity in comparison to patients with a clinical MEN1 diagnosis (8, 9).

The current clinical practice guidelines recommend that patients with MEN1 and their first-degree family members should be offered genetic testing from the age of 5 years. Individuals with a genetic predisposition for developing MEN1-related tumors should be offered periodic clinical screening to detect manifestation in a presymptomatic stage (3). Therefore, genetic counseling and mutation analysis of family members at risk of carrying a MEN1 mutation are of utmost importance. However, genetic testing of the entire family of MEN1 patients is not always performed because not all family members are in contact with the index case, or the physician is not allowed to contact family members directly because of ethical considerations, and some patients simply refuse genetic counseling. Potentially presymptomatic MEN1 mutation carriers can therefore be unaware of their mutational status for a long time. This raises the question whether MEN1-related morbidity and mortality could be reduced in families if genetic counseling and testing in the whole family is immediately performed at the time of diagnosis of the index case.

The primary aim of this nationwide study was to determine the time between the diagnosis of MEN1 in Dutch index cases and the subsequent MEN1 diagnosis in other family members. The secondary aim was to determine the morbidity and mortality associated with this lag time.

Patients and Methods

Patients

In this analysis, all patients from the national MEN1 cohort of the Dutch MEN1 Study Group (DMSG) were included. Patients were diagnosed according to the recently updated clinical practice guidelines (3) if they were aged 16 years or older and were treated at one of the Dutch University Medical Centers (UMCs). In each UMC, MEN1 patients were identified by a standard identification procedure using the hospital diagnosis databases. This longitudinal database with 24 years of follow-up includes > 90% of the total Dutch MEN1 population. Clinical and demographic data were collected by medical record review in a standardized manner using predefined definitions (11, 12). Data of all identified patients were collected from every quarter of every available year of follow-up during the period 1990–2014. Family relationships/trees were documented in the medical records at the department of internal medicine or clinical genetics. Patients were eligible for the present analysis if they had a confirmed MEN1 mutation and had at least one family member with an identical MEN1 mutation. Patients were considered "index" cases if they were the first to be diagnosed with MEN1 within their family. Non-index cases were patients diagnosed with MEN1 because of a previous MEN1 diagnosis of a family member. If patients received a definite MEN1 diagnosis not as a result of family screening, although other family members were already diagnosed with MEN1, they were also considered index cases because they were not diagnosed as a result of family screening. MEN1 patients without family members with a MEN1 diagnosis were not included in this analysis.

Before 1998, the diagnosis of MEN1 was based on clinical criteria; after 1998, patients were mainly diagnosed by direct mutation testing.

The study protocol was approved by the medical ethical committees of all UMCs in The Netherlands. Detailed information on the DMSG database methods was described previously (11).

Statistical analysis

Lag time from index diagnosis

The lag time elapsing between the date of the MEN1 diagnosis of the index case and the date of MEN1 diagnosis in a non-index case (either by genetic testing or clinical diagnosis) in the same family was defined as "lag time" in this study. In a family with more than one index case, the first chronological index case was used to calculate the lag time. For determining the morbidity that arose during the lag time, non-index cases were only included in the analysis if the manifestation of interest was present or not and the lag time could be calculated at the moment of diagnosis.

In 2001, the clinical guideline for diagnosis and therapy of MEN type 1 and type 2 was published (13), and in 2007, the DMSG was founded, a collaboration focused on improving MEN1 research and care in all eight UMCs in The Netherlands. To assess the influence of these changes in the care of patients, the lag time was analyzed per period.

The mean ± SD or median with range was calculated for analysis of the descriptive data. Continuous variables were analyzed by using independent sample *t* test or Mann-Whitney *U* test. Dichotomous variables were compared with logistic regression. Lag time was used as a continuous variable and was defined in years. Because of non-normal distribution, logarithmic transformation of the lag time in years was performed.

Generalized linear mixed model analysis was applied to adjust for clustering within families. Possible confounding was assessed for age. All analyses were conducted using SPSS 21.0 and RStudio version 0.99.441.

Results

Study population

In the period 1990–2014, a total of 393 MEN1 patients were included in the DMSG database, and 58 different MEN1 families with at least two family members were identified. In all families, a MEN1 germline mutation was confirmed, except in one family. The largest family consisted of 25 members with MEN1, and the smallest of two members. In six families, there was more than one index case; the second index case was a family member from another side of the family. Fifty-seven index cases and 247 non-index cases were eligible for the present analysis (n = 304). The index case was diagnosed in 25 (43%) families before mutation testing was available in 1998 and in 33 (57%) families thereafter. Patients who had no family members with MEN1 (n = 89) were not included in this analysis. A total of 57 (18.8%) patients were diagnosed solely because of the presence of two or more clinical manifestations (index cases) without other family members being diagnosed with MEN1.

Non-index cases were diagnosed either in a presymptomatic phase by genetic testing (n = 132) or because of a MEN1-related tumor and a (first-degree) family member with a MEN1 diagnosis (n = 115).

Lag time from index diagnosis and morbidity at time of diagnosis

The median lag time from MEN1 diagnosis of the index cases to the MEN1 diagnosis of their individual family members was 3.5 (range, 0–30) years. The lag time before 1998 was 8 (range, 0–30) years, and from 1998–2001 it was 2.6 (range, 0–15.5) years ($P < .001$) (Table 1). The median lag time from 1998–2001 was longer than the period from 2001–2007, which was 1.4 (range, 0–7.75) years ($P < .001$). The lag time after 2007, the year the DMSG was founded, was 0.75 years ($P = .119$) (Table 1). Only one family, consisting of one index case and two relatives, was diagnosed after the publication of the revised MEN1 management guidelines in 2012. There was no lag time in this family.

A total of 95 (38.4%) non-index cases had pHPT at the moment of the diagnosis of MEN1, and only seven (2.8%) non-index cases had no pHPT. The age-adjusted mean lag times were 9.5 (SD, 8.8) and 3 (SD, 4.1) years, respectively ($P = .035$). Data on pHPT were not available in 13 patients.

Twenty-five (10.1%) non-index cases had a PIT at the moment of MEN1 diagnosis, with a mean lag time of 7.9 (SD, 8.7) years. There was no PIT present at the moment of diagnosis in 181 (73.3%) non-index cases, and in 41 non-index cases the PIT status was not known. Twenty patients had a microadenoma with a mean lag time adjusted for age of 7.2 (SD, 8.7) years, and five had a macroadenoma with a mean lag time of 10.6 years ($P = .0834$). The mean lag time for pituitary macroadenomas with compression of the optic chiasm was 19.9 (range, 19.3–20.5) years, but there were only two family members with chiasmic compression.

Thirty (12.1%) non-index cases had a dpNET with a mean lag time of 7.9 (SD, 8.5) years. There was no dpNET present at the moment of diagnosis in 188 (76.1%) non-index cases, and in 29 non-index cases the dpNET status

Table 1. Median Lag Time From Index Cases to Family Members

Moment Diagnosis of Index Case	Median	Minimum, Maximum	*P*
Total	3.5	0, 30	
Before 1998	8	0, 30	.001
1998–2001	2.6	0, 15.5	
1998–2001	2.6	0, 15.5	.004
2001–2007	1.4	0, 7.75	
2001–2007	1.4	0, 7.75	.119
After 2007	0.75	0, 5.75	

Data represent time in years. 1998 was the year genetic testing for the *MEN1* gene started in The Netherlands. 2001 was the publication date of the Guideline for Diagnosis and Treatment of MEN1 and MEN2. 2007 represents the initiation of the DMSG.

Table 2. Mortality in Non-Index Cases

Case No.	Gender	Age at Diagnosis, y	Cause of Death	Delay[a] in Years
1	Male	63	Metastasized dpNET	2
2	Male	41	Metastasized thymus NET	2.3
3	Male	40	Metastasized thymus NET	2.5
4	Male	55	Metastasized pNET	6
5	Male	75	Metastasized pNET	6.3
6	Male	52	Metastasized NET	10
7	Female	59	Bleeding ZES	15.5
8	Male	46	Metastasized thymus NET	19.3
9	Male	61	Metastasized pNET	20.5
10	Male	74	Metastasized pNET	2.3

Abbreviation: ZES, Zollinger-Ellison syndrome.

[a] Diagnostic delay from index case

was not known. The mean lag time between dpNET smaller and larger than 20 mm was not statistically different ($P = .831$): 8.2 (SD, 8.9) and 7 (SD,7.5) years, respectively. The mean lag time was 10.9 (SD, 12) years in non-index cases (n = 6) with a metastasized dpNET.

Generalized mixed model analyses were applied to adjust for clustering in families, but the logistic regression models without random slopes or intercepts were the models with the best fit in all analyses, according to Akaike's Information Criterion.

Mortality

Ten patients (4%), nine men and one woman, died due to a MEN1-related cause that might have developed before or within in the lag time (Table 2). The manifestation that eventually lead to death was diagnosed at the time of MEN1 diagnosis and not before the MEN1 diagnosis.

Index cases vs non-index cases

The mean age of MEN1 diagnosis of the index cases was higher than the age of diagnosis of the non-index cases: 42 and 34 years, respectively ($P = .001$).

Manifestations at time of MEN1 diagnosis

There were no manifestations present at the moment of the MEN1 diagnosis of the six patients less than 10 years of age. In the 10- to 20-year age group, 12 (20.3%) of the 59 non-index cases had a pHPT, three (5.1%) had a PIT, and three (5.1%) had a dpNET. dpNETs in this age group were smaller than 20 mm, and no metastases were present at the time of diagnosis. In all other age groups, one or more manifestations were present at the moment of MEN1 diagnosis (Table 3).

Fifty-three family members had more than one manifestation at the time of diagnosis. Fifteen family members had more than two manifestations at diagnosis.

A total of 39 family members without a MEN1 diagnosis were under medical care for a pHPT while a family member was already diagnosed with MEN1. Three family members were treated for a dpNET, and two for a PIT with a confirmed MEN1 diagnosis in a family member. Another three patients had more than one related MEN1 manifestation and a family member with MEN1, but they were not identified as MEN1 patients.

Discussion

MEN1 is not only a diagnosis for an individual patient; it also has implications for the patient's whole family. If one family member has a proven mutation in the MEN1 gene, preferably all eligible family members should undergo mutation analysis. In our Dutch MEN1 population, there is a clinically relevant delay in MEN1 diagnosis in families from the moment the index patient is diagnosed with MEN1. The mean lag time in families has significantly decreased since the start of genetic screening in 1998, which can be considered a landmark in the diagnosis of MEN1. Publication of the international guideline in 2001 has led to a further significant decrease in lag time. A decrease of lag time is also seen after 2007, the year the DMSG was founded. After publication of the revised MEN1 management guidelines in 2012, only one new MEN1 family was diagnosed. In this family there was no lag time. A longer follow-up will reveal whether there is a

Table 3. Manifestations at Time of Diagnosis According to Age in Non-Index Cases

Age, y	pHPT	dpNET	PIT	Total
<10	0	0	0	6
11–20	12	3	3	59
21–30	19	3	6	48
31–40	27	4	7	45
41–50	18	8	5	35
51–60	13	8	3	25
>60	12	6	4	21

significant difference between lag times before and after the publication of the revised guidelines. The morbidity in family members, when a lag time is present, ranges from dpNET with metastases, pituitary macroadenomas, and the presence of multiple MEN1 manifestations. Ten patients died because of a manifestation that might have developed within or before the lag time from the index case. These findings suggest that morbidity and mortality can be reduced if more emphasis is placed on genetic counseling and testing of the whole family at the time the index case is diagnosed.

Strengths

To our knowledge, this is the first time the lag time in MEN1 diagnosis from the diagnosis of the index case to diagnosis of other family members has been investigated, as well as the morbidity arising from this lag time. This is therefore a novel way of addressing diagnostic delay in MEN1 patients, which reveals serious clinical consequences.

A major strength of this study is the DMSG database, which consists of > 90% of all MEN1 patients in The Netherlands. This high coverage of MEN1 patients minimizes the occurrence of selection bias. Furthermore, the database contains data from 1990 to 2014 collected every quarter of every year. The long follow-up and high density of the data make this database very suitable and reliable for calculating the lag time to diagnosis of the individual manifestations. All genetic MEN1 analyses were performed at one central location in The Netherlands; therefore, the chance of missing genetic analyses or families is minimal. This database also allowed us to make family trees of all families to identify index cases and their family members.

The lag time was calculated according to the present guideline that recommends that MEN1 germline mutation testing should be offered to first-degree relatives of MEN1 patients at the age of 5 years.

Limitations

It is questionable whether the manifestations developed in the period of the lag time from diagnosis of the index case or whether the manifestations were present before MEN1 was diagnosed in the index cases. However, even if manifestations were present before the MEN1 diagnosis of the index case, one can expect that the manifestations progressed in the lag time. In this view, lag time is still relevant.

Comparison with previous literature

In previous studies, it is acknowledged that early diagnosis of MEN1 reduces morbidity and mortality. Genetic testing and periodical clinical screening may lead to a better clinical outcome (6, 9, 10).

In one study, the age of diagnosis in index cases was significantly higher than in family members, 47.5 vs 38.5 ($P < .001$), respectively (14). We confirmed this finding in our study; however, the ages in both patient groups were lower in our study, namely 42 vs 34 years ($P = .001$), probably reflecting differences in case mix because we report the results of a true national database including > 90% of the total Dutch MEN1 population above the age of 16 years.

Clinical implications

Considering the morbidity and mortality that arise in the lag time, our results imply that all family members of MEN1 patients should be counseled and offered mutation analysis as soon as possible from the moment the index case is diagnosed. A timely start of regular screening in accordance with the guidelines is of equal importance. The guideline recommends to start screening from the age of 5 years, based on the presentation of a pituitary macroadenoma in a child at the age of 5 and pHPT in another child of 5 years of age (15, 16). In our cohort, the six patients younger than 10 years did not have any manifestation at diagnosis. The first manifestations were diagnosed in the 10- to 20-year age group. Considering the low prevalence of manifestations under the age of 10, an informed decision should be made weighing the risks and benefits of starting the screening at such a young age.

Remarkable are the number of patients in care for a MEN1-related manifestation without a MEN1 diagnosis while a family member is already diagnosed with MEN1. This indicates that physicians are often unaware of the possibility of MEN1 causing endocrine diseases and the importance of the family history (4). Evidence-based clinical guidelines can improve awareness and knowledge, but they also offer guidance for clinical practice. After publication of the clinical guideline in 2001, a significant decrease in lag time has been observed in The Netherlands. The implementation and adherence to the guideline has thus been successful. Although not statistically significant, the collaboration of all academic hospitals in the DMSG in 2007 has led to a further decrease of the lag time (1.4 vs 0.75 years). The publication of the guideline and this collaboration have contributed to the awareness of MEN1 by organizing meetings, improving education, and working together in patient care and research. Combining guidelines with educational interventions and making guidelines easy to understand are two important aspects in enhancing the use of guidelines in primary care (17). Primary care providers have indicated that a lack of education and the challenge of keeping up with the guidelines made them

uncertain about guidelines, diagnosis, and treatment. This is especially challenging for a rare disease such as MEN1 because the prevalence in primary care is very low. Meeting with academic mentors to discuss clinical questions and reinforce the guidelines could improve the use of the guidelines (18). Relatives with lag times in this study were receiving both specialist and primary care.

Relatives and their physicians may not have been aware of the presence of MEN1 in their family. Index cases may feel the burden of bringing bad news to the family and consider this as an obstacle. On the other hand, social consequences such as employment and insurance issues could make informed family members reluctant in genetic screening (19). A relevant issue is that the index case might not know all family members, especially if the family is big and not living in the same area. This is illustrated by the finding that in six families more than one index case was identified. Apparently the second diagnosed index case was not aware of the MEN1 diagnosis of the first index case in the family. These families were relatively big with more than 10 family members with MEN1. One can expect that the whole family is at least twice as big and contact between different family members differs.

Ethical considerations such as an individual's right not to know their genetic predisposition as well as their privacy are matters of concern (19). Some authors propose that close family members should receive written information about their risk, even without the consent of the affected MEN1 relatives (19, 20). Considering the morbidity and mortality associated with a delay of MEN1 diagnosis in families, at least this should initiate the discussion with ethical policymakers.

An extension of doctor's delay: lag time from index diagnosis

In the literature, until now more emphasis has been on the lag time between the appearance of the first sign, symptom, or manifestation to the diagnosis of MEN1. This is the so-called doctor's delay. These lag times vary from 7.6 to 17.2 years (7, 9, 21). Proposed reasons for this delay are the lack of acknowledgment of the MEN1 syndrome and the insufficient sharing of medical information about the patients among medical practitioners (14). This is especially relevant for index cases because they are diagnosed solely on clinical grounds. However, family members (non-index cases) outnumber the index cases, and therefore, in our view, more emphasis should be placed on immediate genetic counseling and testing of eligible family members after diagnosis of the index case. There are clinically relevant manifestations when there is lag time; 30 patients had a pNET, of which seven patients already had metastases. The mean lag time for a microadenoma, a macroadenoma, and chiasm compression increases for each stadium, which was 8, 10.6, and 19.9 years, respectively. The difference in lag time was not statistically significant because of the low prevalence of subjects, but a concordant increase could be observed. In conclusion, immediate genetic testing of family members of MEN1 patients and prompt clinical screening according to our MEN1 guidelines will prevent morbidity and mortality and improve long-term outcome in MEN1 patients.

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