Do patients with multiple endocrine neoplasia syndrome type 1 benefit from periodical screening?

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Abstract

Objective: To determine the benefit of periodical clinical screening of carriers of a mutation in the multiple endocrine neoplasia type 1 (MEN-1) gene, because any useful discussion requires more concrete data.

Design and methods: Our study population consisted of all the patients with MEN-1 (n = 58) who were treated at the University Medical Centre Utrecht, The Netherlands, during the period 1975 – 2003, and their affected relatives (n = 29). Records of affected individuals who died were analysed for morbidity, cause of death and age at death. We discuss our results in the light of the literature on MEN-1 regarding the benefit of screening.

Results: Over a period of 28 years, we identified 87 individuals affected with MEN-1, from 16 families. A mutation in the MEN-1 gene was detected in 57%, 18% were obligate carriers, and in 24% the diagnosis was only clinically confirmed. Thirty individuals died, 17 from MEN-1-related causes, including malignancies (n = 12: pancreatic islet cell tumours n = 6 and carcinoid tumours n = 6), the Zollinger–Ellison syndrome (n = 4) and Cushing’s disease (n = 1). The remaining patients died of causes probably related to MEN-1 (n = 3), unrelated to MEN-1 (n = 7) or of unknown causes. Mean ages at death from MEN-1 were 55.4 years for men and 46.8 years for women, in both cases significantly lower than the mean age at death in the average Dutch population (P < 0.05).

Conclusions: We feel that the significantly increased risk of premature death found in patients with MEN-1 justifies the periodical clinical screening of carriers of the MEN-1 gene mutation. Early detection and treatment of abnormalities will probably reduce this risk.

European Journal of Endocrinology 149 577–582

Introduction

Multiple endocrine neoplasia syndrome type 1 (MEN-1) is an autosomal dominantly inherited disorder with a high penetrance and a variable expression (1, 2). MEN-1 is characterised by the combined occurrence of tumours of the parathyroid glands (90–99%), endocrine pancreas/duodenum (65–75%) and the anterior pituitary gland (30–65%) (2–10). Less frequently, adrenal tumours (16–37%) and carcinoid tumours of the thymus (5%), bronchus (8%) or stomach (7%) occur, in addition to angiofibromas (88%), lipomas (34%) and collagenomas (72%) of the skin and leiomyomas of the oesophagus (2%) (6, 7, 11–14). The clinical manifestations can result from hormone hypersecretion, mass effect of tumour growth, malignancy, or any combination thereof. There are no accurate data on the population prevalence of MEN-1, although biochemical data have suggested a prevalence of 2–10 per 100 000 (15).

In 1997, the gene responsible for MEN-1 was identified. This gene, which is presumed to act as a tumour suppressor gene, is located on the long arm of chromosome 11 (11q13) and encodes a protein named menin. In families affected by MEN-1, inactivating germ-line mutations in the MEN-1 gene are responsible for the syndrome (16–18).

So far, no genotype–phenotype correlation has been established in MEN-1 (19, 20). It is believed that the occurrence of somatic or germ-line mutations in unknown modifier genes is important in determining the course of the disease in individual patients with MEN-1 (21).

At present, mutation analysis of the MEN-1 gene is performed in patients who are clinically suspected of having MEN-1, in order to determine the responsible mutation in the MEN-1 gene. If a mutation is detected, relatives can be tested for carriership. Carriers of a mutation in the gene are offered periodical screening. This is believed to decrease morbidity and mortality.
because abnormalities can be detected and treated in an early, often presymptomatic, stage (2, 22–24).

There is currently discussion as to the benefits of periodical screening of affected individuals and the psychological burden placed on them by the screening procedure. This discussion requires more information about the cause of death and age at death in patients with MEN-1.

We have performed a retrospective study in a total of 87 patients with MEN-1, including all those patients with MEN-1 who have attended the University Medical Centre Utrecht over the past 28 years (n = 58), and 29 affected relatives. We determined cause of death and age at death and investigated whether there is a significant difference between the lifespan of patients with MEN-1 and that of individuals who are not affected with MEN-1. We draw conclusions from our results and from the literature on MEN-1 regarding the benefit of screening.

**Materials and methods**

We retrospectively reviewed the records of all patients with MEN-1 who were treated at the University Medical Centre Utrecht (The Netherlands) between January 1975 and July 2003.

With information obtained from municipal archives and interviews with patients and their families, we constructed pedigrees of the patients’ families. Medical information about relatives was obtained from hospital records and family interviews. We considered the diagnosis of MEN-1 was confirmed in patients and relatives who met one of the following criteria:

- Presence of at least three of the five major lesions in an isolated patient: tumours of the parathyroid glands, endocrine pancreas/duodenum, anterior pituitary gland, adrenal glands or neuroendocrine carcinoid tumours.
- Presence of one of the five major lesions in a member of a MEN-1 family. (A MEN-1 family is defined as one in which a patient with MEN-1 has at least one first-degree relative in whom at least one target organ is/was affected (21).)
- Carriers of a mutation in the MEN-1 gene (detected by mutation analysis).
- Obligate disease gene carriers from families in whom a mutation has been detected.

In our hospital, 58 patients with MEN-1 were treated between January 1975 and July 2003. Furthermore, the diagnosis of MEN-1 was confirmed in 29 relatives by DNA analysis or clinical tests and made in cases of obligate carriership. This resulted in a total of 87 patients with MEN-1, belonging to 16 distinct families. A mutation was detected in the MEN-1 gene in all these families. In 50 patients with MEN-1 a mutation was actually demonstrated (57%), whereas 16 patients with MEN-1 were obligate carriers (18%). The remaining 21 patients (24%) were all first-degree relatives of the carriers mentioned above. In these patients, the diagnosis of MEN-1 was clinically assessed, but mutation analysis of the MEN-1 gene was not performed for practical reasons (i.e. these patients either died before mutation analysis became possible, or they refused mutation analysis).

Records of patients with MEN-1 who died were analysed for morbidity, cause of death and age at death. Mortality data were obtained from clinical records and autopsy reports when available.

The mean age at death of patients with MEN-1 who died from MEN-1 was compared (sex-matched) to the mean age at death of the average Dutch population in the period 1975–2001 (using data from Netherlands Statistics). A two-tailed Student’s t-test (P < 0.05) was used to test for significance.

**Results**

**Causes of death**

Thirty patients with MEN-1 died in the 28-year period studied. Of these, 16 deaths were directly related to MEN-1, and one death (patient 6 in Table 1) was most probably related to MEN-1. Furthermore, three patients with MEN-1 probably died of MEN-1-related causes, but we could not determine this with certainty. The cause of death was unknown in three cases, and death was not related to MEN-1 in seven cases. Table 1 shows morbidity, cause of death and age at death of the 17 patients who died of MEN-1-related causes.

Most of the MEN-1-related deaths were the result of malignancy (12 of the 17 deaths; Table 2), including pancreatic islet cell tumours (patients 1, 3, 5, 7, 9 and 12) and carcinoid tumours, arising from the thymus (patients 2, 6, 8 and 11) or the stomach (patient 4), and in one case from an unknown primary tumour (patient 10). Four patients with MEN-1 (patients 13, 14, 16 and 17) died from the Zollinger–Ellison syndrome. One of these patients (No. 14) died early in the study, before Zollinger–Ellison syndrome was treated by histamine receptor or proton pump antagonists. This patient died after having prolonged and complicated peptic ulcer disease. However, the other three patients died from Zollinger–Ellison syndrome more recently. They died unexpectedly, without any clear, preceding symptoms. It was not known earlier that two of these patients (Nos 13 and 17) were affected by MEN-1. One patient in our study died from the consequences of Cushing’s disease (patient 15).

Of the three patients who probably died of MEN-1-related causes, the case history taken from the family suggested that two probably died of a carcinoid tumour of the stomach, although this could not be confirmed. The third patient (aged 79 years) was suffering...
Table 1 MEN-1 lesions, cause of death and age at death of patients who died from MEN-1.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mutation*</th>
<th>Sex (F/M)</th>
<th>Age at death (years)</th>
<th>Cause of death</th>
<th>Other MEN-1 lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>357del4</td>
<td>F</td>
<td>29</td>
<td>Died after operation, after a test laparotomy because of a metastatic islet cell tumour of the pancreas</td>
<td>HPT</td>
</tr>
<tr>
<td>2</td>
<td>357del4</td>
<td>M</td>
<td>39</td>
<td>Metastatic carcinoid of the thymus, infiltration in lung</td>
<td>HPT, metastatic islet cell tumour of the pancreas</td>
</tr>
<tr>
<td>3</td>
<td>357del4</td>
<td>M</td>
<td>72</td>
<td>Metastatic islet cell tumour of the pancreas, infiltration in stomach and spleen</td>
<td>Peptic ulcer disease</td>
</tr>
<tr>
<td>4</td>
<td>357del4</td>
<td>M</td>
<td>64</td>
<td>Carcinoid of the stomach</td>
<td>HPT, glucagonoma causing diabetes</td>
</tr>
<tr>
<td>5</td>
<td>357del4</td>
<td>M</td>
<td>60</td>
<td>Metastatic islet cell tumour of the pancreas, infiltration in stomach and duodenum</td>
<td>HPT, pituitary adenoma, peptic ulcer disease, hyperglucagonaemia causing diabetes</td>
</tr>
<tr>
<td>6</td>
<td>357del4</td>
<td>M</td>
<td>50</td>
<td>Found dead, was suffering from a carcinoid of the thymus with extensive metastases. No autopsy</td>
<td>HPT, prolactinoma, non-functional adrenal adenoma</td>
</tr>
<tr>
<td>7</td>
<td>357del4</td>
<td>M</td>
<td>62</td>
<td>Metastatic islet cell tumour of the pancreas</td>
<td>HPT, microprolactinoma, complicated peptic ulcer disease</td>
</tr>
<tr>
<td>8</td>
<td>465del3</td>
<td>M</td>
<td>65</td>
<td>Metastatic carcinoid of the thymus, infiltration in lung</td>
<td>HPT</td>
</tr>
<tr>
<td>9</td>
<td>Lys362stop</td>
<td>F</td>
<td>49</td>
<td>Metastatic islet cell tumour of the pancreas</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>Lys362stop</td>
<td>M</td>
<td>59</td>
<td>Metastatic carcinoid, unknown primary</td>
<td>HPT, complicated peptic ulcer disease</td>
</tr>
<tr>
<td>11</td>
<td>Lys362stop</td>
<td>M</td>
<td>44</td>
<td>Metastatic carcinoid of the thymus</td>
<td>HPT</td>
</tr>
<tr>
<td>12</td>
<td>Lys362stop</td>
<td>M</td>
<td>47</td>
<td>Metastatic islet cell tumour of the pancreas</td>
<td>HPT, adrenal hyperplasia</td>
</tr>
<tr>
<td>13</td>
<td>Ala385Val</td>
<td>F</td>
<td>36</td>
<td>Perforated duodenal ulcer</td>
<td>–</td>
</tr>
<tr>
<td>14</td>
<td>Ala385Val</td>
<td>M</td>
<td>65</td>
<td>Complicated peptic ulcer disease</td>
<td>HPT</td>
</tr>
<tr>
<td>15</td>
<td>1526insG</td>
<td>M</td>
<td>38</td>
<td>Died after operation, after adrenalectomy because of Cushing’s disease</td>
<td>HPT, two islet cell adenomas in the pancreas, complicated peptic ulcer disease</td>
</tr>
<tr>
<td>16</td>
<td>1778ins8</td>
<td>F</td>
<td>80</td>
<td>Perforated oesophageal ulcer, resulting in a haemorrhagic pleuritis and a complete atelectasis of the left lung</td>
<td>Complicated peptic ulcer disease, islet cell hyperplasia of the pancreas, adrenal cortical hyperplasia, adrenal tumour</td>
</tr>
<tr>
<td>17</td>
<td>1778ins8</td>
<td>F</td>
<td>40</td>
<td>Multiple perforated duodenal and jejunal ulcers</td>
<td>–</td>
</tr>
</tbody>
</table>

* Mutations detected in these patients or in their affected relatives, in case the diagnosis was only clinically assessed. Patients with the same mutations are from the same family, except for patients 1 and 2, who are from another family than patients 3–7.

HPT, primary hyperparathyroidism.
from severe osteoporosis, caused by primary hyperparathyroidism. She fractured her hip, and later died of pneumonia. (Note: this could also have happened had her osteoporosis been simply postmenopausal.)

Causes of death unrelated to MEN-1 were melanoma (n = 2), pulmonary embolism (n = 1), carcinoma of the bladder (n = 1), carcinoma of the lung (n = 1) and cardiovascular disease (n = 2).

Age at death

The male patients with MEN-1 who died of MEN-1-related causes (n = 12) died at a mean age of 55.4 years (range 38–72 years). This mean age at death is significantly lower (P = 0.001) than the average for Dutch men over the same period (70.1 years). The mean age at death of female patients with MEN-1 who died of MEN-1-related causes (n = 5) was 46.8 years (range 29–80 years). This is also significantly lower (P = 0.032) than the mean age at death of the average Dutch women over the same period (75.6 years).

Discussion

In the past, several studies (3, 8–10, 25–28) have considered the cause of death in patients with MEN-1 (see Table 2). The older studies (3, 8, 25) indicated that complications of peptic ulcer disease, or the Zollinger–Ellison syndrome, were the most common cause of MEN-1-related death. In these studies, deaths from malignant pancreatic islet cell tumours account for only 9–13% of the deaths related to MEN-1. Wilkinson et al. (26) were the first to conclude that neoplasm rather than peptic ulcer disease is the main cause of death in MEN-1. Other recent studies (10, 27, 28) have confirmed this conclusion.

In our study, we identified 87 patients with MEN-1, belonging to 16 distinct families. Thirty patients died in the period studied; 17 of them died of MEN-1-related causes. Corresponding to these recent studies (10, 26–28), we found that most of these MEN-1-related deaths were as a result of malignancy (n = 12; 71%), including pancreatic islet cell tumours and carcinoid tumours arising from the thymus and the stomach. Other causes of death were Zollinger–Ellison syndrome (n = 4; 24%) and Cushing’s disease (n = 1; 6%). Three of the patients who died from Zollinger–Ellison syndrome died unexpectedly, without any clear, preceding symptoms. It had not been known earlier that two of these patients were affected by MEN-1. Furthermore, we found that the mean age at death of MEN-1-related causes was 55.4 years for male patients with MEN-1 and 46.8 years for female patients with MEN-1. In both cases, this is significantly lower than the mean age at death in the average Dutch population. These findings demonstrate the need for early identification of patients with MEN-1 and those who are carriers, in addition to the importance of clinical screening and treatment if necessary.

Our study differs from previous studies in that a mutation in the MEN-1 gene had actually been demonstrated in most of our patients. Furthermore, in most of the living relatives affected with MEN-1 who were included in our study, MEN-1 carriage was identified by mutation analysis and not by expression of the disease, as in the previous studies. As a result, the probability of having included non-carriers of MEN-1 (false positives) in our study, in addition to the preselection of patients with MEN-1 with obvious clinical manifestations, compared with MEN-1 gene mutation carriers with non-penetrance, may be smaller than in previous studies.

The reliability of our conclusions, in addition to those in the other studies, is influenced by several factors. First,
we are dealing with only a small number \((n = 17)\) of patients who died of MEN-1-related causes, so that individual cases exert a large influence on the study outcome. Secondly, MEN-1 has a variable expression. Thirdly, methods of diagnosis and treatment have improved considerably over the past few decades, changing the course of the disease. Some of the patients who died early on in the period studied might well have survived today. Thus our patients make up a heterogeneous group.

Genetic and clinical screening is generally believed to be necessary in MEN-1 families. Genetic screening provides certainty to patients and relatives and it means non-affected individuals do not have to undergo time-consuming and expensive periodical clinical investigations. Clinical screening is performed in carriers of the MEN-1 gene mutation and aims at detecting abnormalities at a presymptomatic stage. This is possible because most MEN-1-related abnormalities can be detected by biochemical tests several years before they become clinically overt \((5, 20)\). Detecting and treating abnormalities at an earlier stage results in less morbidity \((5)\) and is likely to reduce mortality resulting from malignancies, because the development or progression of the malignancy may be prevented \((12, 29, 30)\). Furthermore, our research shows that the probability of dying unexpectedly as a result of MEN-1 or complications arising from it is smaller if clinical screening is conducted.

In our opinion, MEN-1 follows, in general, a rather benign course: at present most patients with MEN-1 reach an old age without any serious or life-threatening complications of the disorder. However, in some patients, MEN-1 is treacherous: thymic carcinoids and non-functioning pancreatic islet cell tumours cause symptoms for the first time at a late stage of the disease. Then, cure is only rarely possible and patients die at a significantly younger age than unaffected individuals. For this reason, we feel it is fully justified to recommend periodical screening of all carriers of mutations of the MEN-1 gene.

Nevertheless, at present, most screening programmes for hereditary endocrine tumour syndromes in most countries are of only a temporary nature. We feel strongly that the clinical screening of MEN-1 gene mutation carriers should be performed on a structured basis, and a national service should therefore be established.

Acknowledgements

We thank the following collaborators and institutions for providing patient material and clinical data: Dr B Bravenboer (Catharina Hospital, Eindhoven), Dr FH Menko (Free University Medical Centre, Amsterdam), Dr JM Sepers (Medical Centre, Alkmaar), and the Department of Medical Administration of Medical Centre Alkmaar. We also thank R Bongers, G Rabelink and BG Smith for their excellent technical assistance, JM Jansen-Schillhorn van Veen for data research, and Dr MR Canninga for re-evaluation of histological specimens. We are indebted to JL Eriksen and Dr JW Hoppenner for reading the manuscript. We are especially grateful to our patients and their families for their contribution.

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