CLINICAL STUDY

Shortness: an unknown phenotype of multiple endocrine neoplasia type 1

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Abstract

Objective: An observation of shortness among the female participants of a regular screening program in multiple endocrine neoplasia type 1 (MEN1) patients has raised the question as to whether shortness represents a phenotype characteristic of the disease.

Methods: The body height (cm) of genetically confirmed MEN1 patients at the time of diagnosis was compared with the body height of their unaffected relatives (parents, siblings, and children), the mid-parental body height, and the body height of the age-matched German population. Univariate analysis of the clinical variables was performed using the *t*-test, Mann–Whitney *U* test, and ANOVA as appropriate, and multivariate analysis was performed as a logistic regression analysis. *P* values <0.05 were considered statistically significant.

Results: The mean body height of 22 female MEN1 patients (mean age 33.5 years) was 161 ± 5 cm and thus significantly lesser than the body heights of their unaffected female relatives (mean 165.5 ± 7.3 cm, *P*=0.027) and the age-matched German female population (mean 167 cm, *P*=0.0001) and mid-parental height (177.5 cm, *P*<0.0001). The mean body height of 24 male MEN1 patients (mean age 34.8 years) was also lesser (177 ± 6.5 cm) than the average body height of German males in this age group (180 cm, *P*=0.031) and tended to be lesser than that of their unaffected male relatives (178.5 ± 5.8 cm, *P*=0.0915) and the mid-parental body height (177.5 cm, *P*=0.124).

Conclusions: Small body height is a yet unrecognized phenotype characteristic of MEN1 patients, especially in women. The mechanisms behind this phenotypical characteristic warrant further investigation.

European Journal of Endocrinology 169 133–137

Introduction

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant inherited familial tumor syndrome with a prevalence ranging from 1 in 10 000 to 1 in 100 000 (1, 2). It is characterized by the occurrence of multiple neoplastic endocrine lesions, including primary hyperparathyroidism, pituitary neoplasms (mostly prolactinomas), and pancreaticoduodenal neuroendocrine neoplasms (pNENs) (2, 3). Adrenal lesions are also quite common with an incidence of ~50% (4). Neuroendocrine neoplasms of the thymus, lung, or stomach may also occur as well as cutaneous lesions such as lipomas and fibromas (3, 5). The penetrance of the MEN1 syndrome is ~100% by the age of 50 years (2, 3). Besides thymic carcinoids, pNENs are the most common disease-related cause of death in MEN1 because all pNENs have the biological ability to develop distant metastases (6, 7).

The discovery of causative germline mutations in the *MEN1* gene on chromosome 11q13 in 1997 (8) allows a predictive genetic screening to identify the mutation carriers and to include these patients in screening programs. Over 1000 different germline mutations in the *MEN1* gene have been described so far (9, 10, 11). The *MEN1* gene is a tumor suppressor gene and encodes for the protein menin. Numerous studies have suggested an important role for menin in the regulation of gene transcription, cell proliferation, genome stability, and apoptosis. However, the precise underlying mechanisms that are required to explain the functions of the protein and the endocrine-specific nature in MEN1 patients remain still unexplained (12, 13, 14, 15, 16, 17).

During a standardized prospective MEN1 screening program at our institution (18, 19), we got the impression that MEN1 patients might be smaller in body height than both their unaffected relatives and the

age-matched German average population. To date, there have been no reports in the literature concerning the body height of MEN1 patients. Thus, the aim of this study was to evaluate the hypothesis that small body height might be a yet unrecognized phenotype characteristic of MEN1 patients.

Subjects and methods

Between 1987 and 2012, 65 MEN1 patients of 39 families were treated at the Department of Surgery, University Hospital Marburg (Germany). The diagnosis of MEN1 was based on a careful investigation of personal and family history and the identification of a germline mutation in the *MEN1* gene. Since 1997, the presence of MEN1-associated tumors has been assessed by an annual routine screening program, including biochemical analysis and imaging techniques (18, 19). All data were prospectively collected with special regard to patient demographics, clinical features, laboratory findings, imaging, operative procedures, pathologic findings, and follow-up.

Based on physical appearance, shortness was considered a potential phenotype of MEN1 patients. Therefore, we measured the body height of all 65 MEN1 patients during their hospital stay by a standardized measurement. The height of the patients was measured with them standing barefoot straight along a wall with a wall-fixed body height meter. The height of the unaffected relatives (siblings, parents, and children) of the patients was measured when they visited them in the hospital in the same way or they were contacted to measure their body height after a standardized protocol (standing barefoot straight before a wall). The height of all the patients was measured and recorded in centimeters. The height was measured in 0.5 cm intervals. For the present analysis, only families with measured body heights of the affected and unaffected family members were considered.

The average height with the corresponding s.d. of the population living in Germany was obtained from the results of the German National Health Interview and Examination Survey 2009 (20). Female MEN1 patients were also interviewed regarding the first occurrence of

their menarche and compared with the average German female population from 2007 (21).

Descriptive and explorative statistics were performed using mean, median, range, and s.d.; univariate analysis of the clinical variables was performed using the *t*-test, Mann–Whitney *U* test, and ANOVA as appropriate. Multivariate analysis was performed using a multistep logistic regression model with a stepwise selection procedure to analyze the association of body height with the presence of, e.g. pituitary disease, parathyroid disease, and pNENs, the presence of a heavy disease burden (three or more affected organs), and the underlying germline mutation. The variables associated with *P* < 0.20 in the univariate analysis were included in the multivariate logistic regression analysis. The final model included variables at the level of *P* ≤ 0.05.

P values < 0.05 were considered statistically significant. Univariate and multivariate analyses were performed using the SPSS Software version 16 (SPSS, Inc.).

Results

The body height of 46 MEN1 patients and 138 (mean 3.1 per family) unaffected close relatives (parents, siblings, and children) of 39 different MEN1 families was measured. All of these patients were full-grown adults at the time of diagnosis, so they were included in the analysis. All patients except one Spanish male patient and his son and one woman from Asia were born and raised in Germany. The clinical characteristics of these patients are listed out in Table 1.

Female patients

Twenty-two (48%) female patients with a mean age of 33.5 years (s.d. ± 9 years) at diagnosis had a mean body height of 161 cm (s.d. ± 5 cm). Comparison between the female MEN1 patients and their unaffected female relatives (mother, sisters, and daughters) revealed that the unaffected female relatives (mean 2.3 per family; s.d. ± 1.1) had a mean body height of 165.5 ± 7.3 cm, which was significantly (*P* = 0.027) greater than the body height of their affected relatives (Fig. 1; Table 2).

Table 1 Clinical characteristics of the analyzed MEN1 patients.

	All patients (n=46)	Female patients (n=22)	Male patients (n=24)
Genetically confirmed	43/46 (93%)	21/22 (95%)	22/24 (92%)
Age at diagnosis (mean ± s.d.)	33.9	33.5 ± 9.28	34.8 ± 13.16
Clinical manifestations			
pHPT	43/46 (93%)	22/22 (100%)	21/24 (87.5%)
pNENs	41/46 (89%)	21/22 (95%)	20/24 (83%)
Prolactinoma	13/46 (28%)	6/22 (27%)	7/24 (29%)
Others ^a	5/46 (11%)	3/22 (14%)	2/24 (8%)

MEN1, multiple endocrine neoplasia type 1; pHPT, primary hyperparathyroidism; pNENs, pancreaticoduodenal neuroendocrine neoplasms.
^aE.g. NEN of the thymus or bronchus.

Figure 1 Body heights of the female MEN1 patients (circles), unaffected female relatives (triangles), and average age-matched German female population (squares). German average taken from the results of the German sample census 2009 (20). MEN1+, patients with multiple endocrine neoplasia 1; MEN1–, women without MEN1.

In addition, the body height of the female MEN1 patients was also significantly lesser than the mid-parental height (177.5 ± 3.8 cm, $P < 0.0001$).

Comparison of the mean body height (161 cm) of the female MEN1 patients with the average height of the German female population aged between 30 and 35 years from the sample census in 2009 (age group: 30–40 years = 167 cm) also revealed a highly significant difference ($P = 0.0001$) (Table 2).

Only 15 (68%) female MEN1 patients were able to accurately recall the first occurrence of menarche. Menarche occurred at a mean age of 13 ± 1.3 years, which was equal to that of the average German female population from 2007 (12.9 years).

Data on GH levels at the time of first presentation were only available for four patients, but were all within normal limits.

Table 2 Body heights of the MEN1 patients, unaffected relatives, and age-matched average German population.

	<i>n</i>	Body height (cm)	<i>P</i> value
Women			
Female MEN1 patients	22	161 ± 5	
Unaffected female relatives	78	165.5 ± 7.3	0.027
Mid-parental		177.5 ± 3.8	< 0.0001
German age-matched female population ^a		167.0	0.0001
Men			
Male MEN1 patients	24	177 ± 6.5	
Unaffected male relatives	61	178.5 ± 5.8	0.0915
Mid-parental		177.5 ± 3.8	0.124
German age-matched male population ^a		180.0	0.031

^aResults from the German sample census 2009 (20).

Male patients

Twenty-four (52%) male MEN1 patients with a mean age of 34.8 ± 13.2 years at diagnosis had a mean body height of 177 ± 6.5 cm (Table 2). Comparison of the male MEN1 patients with their unaffected male relatives (father, brothers, and sons) revealed that the unaffected family members (mean 2.2 per family, s.d. ± 0.9) tended to be taller (178.5 ± 5.8 cm, $P = 0.0915$). The body height of the male MEN1 patients on comparison with the mid-parental height (177.5 cm + 4.2, $P = 0.124$) showed no statistical difference. The mean body height (180 cm) of the German male population aged between 30 and 35 years from the German sample census in 2009 was, however, significantly greater ($P = 0.031$). Data on the GH levels at the time of first presentation were available for three patients and were all within normal limits.

Given the range of disease and demographic variables, we performed a multivariate analysis to identify possible associations between clinical characteristics and body height. However, the analysis showed no significant association between body height and the presence of pituitary disease, parathyroid disease, or GEP NENs, the presence of a heavy disease burden (three or more affected organs), an early onset of the disease, and the underlying germline mutation respectively.

Discussion

This is the first study to demonstrate that MEN1 patients are smaller than the average German population (females: 6 cm, $P = 0.0001$; males: 3 cm, $P = 0.031$). Most importantly, we could show that MEN1 patients are also smaller than their unaffected relatives. For the female MEN1 patients, the difference was statistically significant (4.5 cm, $P = 0.027$); for the male MEN1 patients too there was a similar tendency (1.5 cm, $P = 0.0915$). Despite the small sample size, the significance underscores the clinical observation that shortness may represent a true phenotypic characteristic of MEN1 patients.

Since the first description of the MEN1 syndrome (22, 23) and the identification of the underlying mutation in 1997 (8), the knowledge regarding the molecular, biochemical, and clinical characteristics of this syndrome has evolved. However, concerning the body height in these patients, there are as yet no publications that have paid attention to this special issue. A literature research revealed only one report that had described a 5-year-old male MEN1 patient with accelerated growth due a pituitary macroadenoma (24).

Support for our clinical study comes from preclinical studies. Nearly 10 years ago, Bertolino *et al.* (25) reported one of the first genetically engineered mouse models of MEN1. In this study, they showed that a large

proportion of MEN1 embryos were generally smaller in size. The authors suggested a link between menin and telomere function and that the loss of menin may affect telomere-mediated cellular function, resulting in earlier senescence.

One can only speculate about the pathophysiological mechanisms, which might cause an earlier termination of growth within the MEN1 patients. Early puberty of MEN1 patients could be a possible mechanism to explain the present observation. Unfortunately, in the present patient cohort, it was not possible to determine the time when puberty began. Considering menarche as an indirect marker for maturation, no difference in the average German female population from 2007 was observed (mean 13 vs 12.9 years) (21).

It is conceivable that the production and/or secretion of GHs and/or sex hormones might be disturbed in patients with MEN1. Unfortunately, there are no data regarding the GH levels of MEN1 patients during childhood to confirm this assumption. In the evaluated cohort, the GH levels (somatotropin, insulin-like growth factor 1, and GHRH) were only available in 15% of the patients, but normal in all the female and male patients tested.

Another possible explanation for the reduced body height in MEN1 patients could be the inadequate effect of GHs due to a disturbed signal transduction. Numerous studies have suggested an important role for menin in the regulation of gene transcription, cell proliferation, genome stability, and apoptosis. *In vitro* studies have shown that menin interacts not only with transcriptional factors such as *JUND* and *NF-κB* (*NFKB1*), but also with proteins involved in the regulation of DNA repair (RPA2, kinases, and ASK (DBF4)) and cytoskeletal proteins (e.g. vimentin) (12, 13, 14, 15, 16, 17, 26, 27). The precise functions of the menin protein are yet to be uncovered (12, 13, 14, 15, 16, 17, 26, 27). Thus, it is highly speculative to draw a direct link between the function of menin and the possible phenotypic characteristic of small body height in MEN1 patients.

The present study is limited by its monocentric design and the small sample size. A large-scale multicentric study is needed to confirm the present observation and potentially uncover the underlying mechanisms.

Declaration of interest

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

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Acknowledgements

The authors are grateful to all the patients who participated in the study.

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Received 2 September 2012

Accepted 2 May 2013