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ORIGINAL ARTICLE

Clinical presentation of MEN 2A in index vs. non-index patients

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Abstract

Purpose Differences in syndromic manifestations of multiple endocrine neoplasia 2 A (MEN2A) between index and non-index patients are ill-defined.

Methods Cross-sectional analysis of 602 *RE*arranged during *T*ransfection (*RET*) carriers (156 index and 446 non-index patients) who underwent thyroidectomy, adrenalectomy, and/or parathyroidectomy between 1985 and 2022, stratified by mutational risk.

Results Index patients were 5.8–13.9 years older at thyroidectomy than non-index patients, at which point they had developed 10.6–14.4 mm larger medullary thyroid cancers. Correlations between index status and primary tumor size ($\rho = 0.489$–0.544) were stronger than correlations between index status and age at thyroidectomy ($\rho = 0.359$–0.438). For pheochromocytoma and primary hyperparathyroidism, no significant differences were noted. When stratified by time of surgery before vs. in the new millennium, age at thyroidectomy fell significantly only for non-index patients in the new millennium: from 28.6 to 21.2 years (moderate–high risk mutations; $P = 0.049$) and from 23.1 to 12.3 years (high-risk mutations; $P < 0.001$). All other inter-millennium comparisons did not reach statistical significance.

Conclusion These findings imply that differences between index and non-index patients impact the first syndromic manifestation without extending to subsequent syndromic manifestations. Because they exhibited similar age and tumor characteristics for the secondary and tertiary manifestations of MEN2A, screening for these syndromic components remains an integral element of MEN2A management in index and non-index patients alike. Wider use of population genomic screening may work to diminish the observed disparities between index and non-index patients going forward.

Keywords Multiple endocrine neoplasia type 2 A · Index patient · Medullary thyroid carcinoma · Pheochromocytoma · Primary hyperparathyroidism

Introduction

The '*index patient*', also referred to as *'index case', 'proband'* or '*propositus/proposita*', is the individual whose genetically transmitted condition is first identified in a family, prompting screening within that family for the trait. Relatives identified as affected on family screening are referred to as '*non-index patients*'. Differences in syndromic manifestation of monogenic disease that may exist between index and non-index patients are not well defined.

Owing to its infrequency and heterogeneity, it has been difficult to collect standardized disease information about multiple endocrine neoplasia type 2A (MEN2A). MEN2A is an autosomal dominant syndrome composed of medullary thyroid cancer (MTC; first syndromic manifestation), pheochromocytoma (second syndromic manifestation) and primary hyperparathyroidism (third syndromic manifestation) [1–4]. As per *Revised American Thyroid Association Guidelines for the Management of Medullary Thyroid Carcinoma*, *RE*arranged during *T*ransfection (*RET*) mutations fall into a high risk category (p.Cys634; classic MEN2A) and a moderate risk category [5]. The latter category can be subdivided into a moderate–high risk category (p.Cys609, p.Cys611, p.Cys618, p.Cys620 and

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p.Cys630, incomplete MEN2A) and a low–moderate risk category (p.Glu768Asp, p.Leu790Phe, p.Val804Leu, p.Val804Met and p.Ser891Ala, predominantly MTC only) [1]. Remarkably, these hot spot germline mutations are dispersed fairly equally around the globe [6].

Science is informed by what it is possible to measure, and it takes a great leap forward when something new can be measured [7]. This also hold true for MEN2A, for which a large body of clinical and genomic data has accumulated over the past 30 years.

The goal of the present study was to quantify, for the first time, differences in syndromic manifestations of MEN2A between index and non-index patients, with an emphasis on primary tumor size and age at surgery as key measures.

Patients and methods

The present research was performed in accordance with the amended Declaration of Helsinki and relevant local rules (institutional review board approval reference 2020-237). All carriers of *RET* mutations (http://www.arup.utah.edu/database/MEN2/MEN2_display.php) [8] had surgical interventions under informed consent for at least one syndromic MEN2A component. Patients who did not undergo central node dissection or did not have evidence of node metastasis on pathological examination were considered to be free of node metastasis after revealing normal postoperative calcitonin serum levels. Adrenalectomy for imaging-positive pheochromocytoma, and parathyroidectomy for primary hyperparathyroidism were carried out at the attending physician's and surgeon's discretion. All procedures, including genetic counseling and screening for *RET* mutations after informed consent, complied with national and international clinical standards applicable at the time of surgery [5, 9, 10].

Included this study were all carriers of pathological missense *RET* variants (hereinafter referred to as mutations) who underwent thyroidectomy, adrenalectomy and/or parathyroidectomy under the direction of the senior author since 1985 [4, 11–13]. Also considered were these carriers' next of kin managed elsewhere for whom information about age at surgery and histopathological results was available.

MTC was diagnosed upon evidence of extension beyond the basement membrane and/or, demonstration of lymphatic or vascular invasion on histopathological analysis.

Pheochromocytoma was diagnosed when plasma free metanephrines and normetanephrines or 24-hour urine metanephrines and normetanephrines were raised and a zellballen pattern was present on definitive histopathology.

Primary hyperparathyroidism was diagnosed in the presence of increased albumin corrected calcium or ionized serum calcium measurements together with increased intact parathyroid hormone serum levels, which normalized after removal of one or more enlarged parathyroid glands. Parathyroidectomy was performed only for enlarged parathyroid glands when serum calcium and parathyroid hormone levels were clearly raised.

For statistical analysis, the software package SPSS® version 28 (IBM, Armonk, New York, USA) was used. Continuous data were tested with univariate analysis of variance (ANOVA) and student t test, as appropriate. Missing data were not replaced, and the number of individuals analyzed is provided for each variable examined. Correlations between continuous variables were evaluated with Spearman's rank sum test. Statistical significance (all results were two-tailed) was set at $P < 0.05$.

Results

All in all, 602 MEN2A carriers, 156 index and 446 non-index patients, of whom 341 were female and 261 male, met the inclusion criteria. Altogether, 470 carriers, 120 index and 350 non-index patients, underwent standard MEN2A-related interventions at the authors' institution, whereas 132 relatives, 36 index and 96 non-index patients, had sufficiently detailed clinicopathological information for analysis.

In total, 233 carriers (38.7%) harbored high risk mutations, 167 carriers (27.7%) moderate–high risk mutations, and 202 carriers (33.6%) low–moderate risk mutations.

Table 1 gives the breakdown of all 602 study patients by index status.

Index patients were older at thyroidectomy (means of 45.4 vs. 30.5 years; $P < 0.001$), had more often developed MTC (97.4 vs. 57.0%; $P < 0.001$), larger thyroid tumors (means of 19.5 vs. 7.9 mm; $P < 0.001$), and more often node metastases (71.5 vs. 29.5%; $P < 0.001$) than non-index patients, resulting in less frequent biochemical cure (34.1 vs. 74.8%; $P < 0.001$).

At last follow-up, index patients were also older (means of 50.6 vs. 27.7 years; $P < 0.001$) and thus had developed more often pheochromocytoma (30.1 vs. 13.2%; $P < 0.001$) and primary hyperparathyroidism (9.0 vs. 3.8%; $P = 0.019$).

In spite of this, pheochromocytoma size and age at first adrenalectomy, and age at parathyroidectomy were comparable among index and non-index patients.

Among index and non-index patients, low–moderate, moderate–high, and high *RET* risk categories were not sufficiently balanced, necessitating stratification by *RET* risk category in subsequent analyses.

Table 2 shows that index patients were 5.8–13.9 years older at thyroidectomy than non-index patients, at which point they had developed 10.6–14.4 mm larger MTCs, irrespective of *RET* risk category. Correlations between index status and primary tumor size (Spearman's $\rho = 0.489$–0.544; Table 2, rows, upper panel) were closer than correlations between index status and age at

Table 1 Baseline characteristics of index vs. non-index patients in MEN 2A

Variables		Index (156 carriers)	Non-index (446 carriers)	*P*
Sex	male, *n*	61 (39.1)	200 (44.8)	0.224
Medullary thyroid cancer	No. of carriers	152 (97.4)	254 (57.0)	<0.001
	Age at thyroidectomy for MTC, yrs, mean [95% CI]	45.4 [42.8; 47.9] ($n = 152$)	30.5 [28.1; 32.8] ($n = 254$)	<0.001
	Largest primary tumor diameter, mm, mean [95% CI]	19.5 [16.8; 22.1] ($n = 120$)	7.9 [6.6; 9.1] ($n = 201$)	<0.001
	No. of carriers with node-positive MTC	98 (71.5) ($n = 137$)	67 (29.5) ($n = 227$)	<0.001
	No. of carriers with biochemical cure	42 (34.1) ($n = 123$)	157 (74.8) ($n = 210$)	<0.001
First pheochromocytoma	No. of carriers	47 (30.1)	59 (13.2)	<0.001
	Age at adrenalectomy, yrs, mean [95% CI]	37.5 [34.1 ; 41.0] ($n = 46$)	35.7 [32.5; 38.8] ($n = 59$)	0.431
	Largest primary tumor diameter, mm, mean [95% CI]	37.2 [29.8; 44.7] ($n = 20$)	40.7 [33.9; 47.5] ($n = 36$)	0.505
Primary hyperparathyroidism	No. of carriers	14 (9.0)	17 (3.8)	0.019
	Age at parathyroidectomy, yrs, mean [95% CI]	40.9 [33.7; 48.0] ($n = 14$)	36.4 [29.3; 43.4] ($n = 17$)	0.348
Follow-up	Age at most recent follow-up, yrs, mean [95% CI]	50.6 [48.0; 53.1]	27.7 [25.8; 29.5]	<0.001
RET risk category[a], no. of carriers	low–moderate	70 (44.9)	132 (29.6)	0.002
	moderate–high	39 (25.0)	128 (28.7)	
	high	47 (30.1)	186 (41.7)	

Owing to rounding, not all numbers add up

CI confidence interval, *MTC* medullary thyroid cancer, *RET* rearranged during transfection, *Ala* alanine, *Arg* arginine, *Asp* aspartic acid, *Cys* cysteine, *Glu* glutamic acid, *Gly* glycine, *His* histidine, *Leu* leucine, *Phe* phenylalanine, *Ser* serine, *Trp* tryptophan

[a]Low–moderate risk: p.Glu768Asp, p.Leu790Phe, p.Val804Leu/Met, p.Ser891Ala

Moderate–high risk: p.Cys609/611/618/620/630Arg/Gly/Phe/Ser/Tyr

High risk: p.Cys634Arg/Gly/Phe/Ser/Trp/Tyr

thyroidectomy (Spearman's $\rho = 0.359$–0.438; Table 2, rows, lower panel).

Conversely, correlations between *RET* risk categories and age at thyroidectomy were stronger (Spearman's $\rho = -0.450$ to -0.606) than correlations between *RET* risk categories and primary tumor size (Spearman's ρ non-significant and 0.245; Table 2, columns).

For pheochromocytoma and primary hyperparathyroidism, no statistically significant differences were noted (Table 3).

When stratified by time of surgery before vs. in the new millennium, age at thyroidectomy fell significantly only for non-index patients in the new millennium: from 28.6 to 21.2 years (moderate–high risk category; $P = 0.049$) and from 23.1 to 12.3 years (high risk category; $P < 0.001$). All other inter-millennium comparisons did not reach statistical significance.

Discussion

This investigation is the first study to provide quantitative information about the syndromic manifestation of MEN2A separately for index and non-index patients. Herein, significant associations were noted exclusively for the earliest (MTC), but not for subsequent MEN2A manifestations (pheochromocytoma and primary hyperparathyroidism). Remarkably, primary tumor diameter, which may have facilitated the diagnosis of MTC, was correlated more closely with index status than with age at thyroidectomy. This illustrates the crucial role of genomic and biochemical screening in narrowing down disparities between index and non-index patients and depleting the pool of hidden *RET* carriers destined to become index patients, unless caught early-on.

Cross-sectional studies, which are limited to a single point in time, reveal the clinical features of a group of people at a specific age [4]. The present research, encompassing 602 *RET* carriers, has several limitations due to the retrospective design and the long study period spanning several decades, reflecting medical progress with the shift from reactive to preventative medicine [4].

Not all *RET* carriers managed outside the authors' institution had complete or accessible clinical records, and follow-up intervals were variable in past decades. Because all *RET* carriers underwent thyroid surgery at the authors' institution or elsewhere, differences in length of observation between

Table 2 Primary tumor size and age at thyroidectomy in index vs. non-index patients stratified by *RET* risk category

Tumor type	Variable	*RET* risk category*	Index status			*P*	ρ
			Index	Non-index	Difference		
Medullary thyroid cancer	Largest primary tumor diameter, mm, mean [95% CI]	low–moderate	16.0 [12.2; 19.7] ($n = 58$)	5.4 [3.8; 7.0] ($n = 57$)	10.6 [6.5; 14.6]	<0.001	0.544
		moderate–high	23.2 [18.4; 28.0] ($n = 24$)	10.6 [7.3; 13.9] ($n = 47$)	12.6 [7.0; 18.2]	<0.001	0.502
		high	22.4 [17.1; 27.8] ($n = 38$)	8.0 [6.2; 9.9] ($n = 97$)	14.4 [8.7; 20.1]	<0.001	0.489
		P	0.042	0.014			
		ρ	0.245	–			
	Age at thyroidectomy, yrs, mean [95% CI]	low–moderate	55.3 [52.3; 58.3] ($n = 68$)	41.4 [37.2; 45.6] ($n = 59$)	13.9 [8.8; 19.1]	<0.001	0.438
		moderate–high	41.9 [37.4; 46.4] ($n = 37$)	36.1 [31.6; 40.6] ($n = 68$)[a]	5.8 [−1.0; 12.7]	0.094	–
		high	33.7 [30.2; 37.2] ($n = 47$)	22.4 [19.4; 25.4] ($n = 127$)[b]	11.3 [6.7; 15.8]	<0.001	0.359
		P	<0.001	<0.001			
		ρ	−0.606	−0.450			

CI confidence interval, *RET rearranged during transfection, Ala* alanine, *Arg* arginine, *Asp* aspartic acid, *Cys* cysteine, *Glu* glutamic acid, *Gly* glycine, *His* histidine, *Leu* leucine, *Phe* phenylalanine, *Ser* serine, *Trp* tryptophan

*Low–moderate risk: p.Glu768Asp, p.Leu790Phe, p.Val804Leu/Met, p.Ser891Ala

Moderate–high risk: p.Cys609/611/618/620/630Arg/Gly/Phe/Ser/Tyr

High risk: p.Cys634Arg/Gly/Phe/Ser/Trp/Tyr

[a]Means of 21.2 yrs in the new millennium vs. 28.6 years before the new millennium ($P = 0.049$)

[b]Means of 12.3 yrs in the new millennium vs. 23.1 years before the new millennium ($P < 0.001$)

ρ: Spearman's rank correlation coefficient rho

Table 3 Primary tumor size and age at adrenalectomy and parathyroidectomy in index vs. non-index patients stratified by *RET* category

Tumor type	Variable	*RET* risk category[a]	Index status			*P*
			Index	Non-index	Difference	
First pheochromocytoma	Largest primary tumor diameter, mm, mean [95% CI]	low–moderate	31 ($n = 1$)	37.3 [4.4; 70.3] ($n = 3$)	−6.3 [−72.3; 59.6]	0.720
		moderate–high	33.2 [17.6; 48.8] ($n = 6$)	35.8 [14.9; 56.8] ($n = 6$)	−2.7 [−25.3; 20.0]	0.798
		high	39.5 [29.2; 49.9] ($n = 13$)	42.2 [33.9; 50.5] ($n = 27$)	−2.6 [−16.1; 10.9]	0.699
		P	0.688	0.445		
	Age at adrenalectomy yrs, mean [95% CI]	low–moderate	46.0 ($n = 2$)	32.3 [20.9; 43.6] ($n = 4$)	13.8 [−140.3; 167.8]	0.524
		moderate–high	40.7 [34.3; 41.1] ($n = 14$)	39.6 [34.4; 44.8] ($n = 13$)	1.1 [−6.8; 9.0]	0.777
		high	35.5 [31.3; 39.7] ($n = 30$)	34.8 [30.7; 38.9] ($n = 42$)	−0.7 [−5.2; 6.6]	0.818
		P	0.222	0.383		
Primary hyperparathyroidism	Age at parathyroidectomy, yrs, mean [95% CI]	low–moderate	43 ($n = 1$)			N/A
		moderate–high	49.0 ($n = 2$)	48.5 [4.0; 93.0] ($n = 2$)	0.5 [−74.2; 75.2]	0.980
		high	39.1 [31.7; 46.7] ($n = 11$)	34.7 [27.2; 42.3] ($n = 15$)	4.4 [−5.6; 14.5]	0.370
		P	0.754	0.676		

Owing to rounding, not all numbers add up

CI confidence interval, *N/A* not assessable, *RET rearranged during transfection, Ala* alanine, *Arg* arginine, *Asp* aspartic acid, *Cys* cysteine, *Glu* glutamic acid, *Gly* glycine, *His* histidine, *Leu* leucine, *Phe* phenylalanine, *Ser* serine, *Trp* tryptophan

[a]Low–moderate risk: p.Glu768Asp, p.Leu790Phe, p.Val804Leu/Met, p.Ser891Ala

Moderate–high risk: p.Cys609/611/618/620/630Arg/Gly/Phe/Ser/Tyr

High risk: p.Cys634Arg/Gly/Phe/Ser/Trp/Tyr

index and non-index patients, conceptually, should not impact ascertainment of MTC, the first disease manifestation. By way of contrast, non-index patients who were younger at last follow-up may not have been given the same amount of time than index patients to develop secondary MEN2A manifestations, notably pheochromocytoma and primary hyperparathyroidism. This reasoning explains the lower event rates for non-index patients relative to index patients (Table 1). Of

note, key measures of hereditary disease, primary tumor size and age at surgery, were prospectively registered and are extremely robust to temporal change.

That said, the retrospective study design, overcoming issues of limited statistical power for rarer disease manifestations [14], enabled collection of a large sample size of rare *RET* mutations which would be difficult, if not impossible, to collect and assess prospectively using Kaplan-Meier time-to-event methodology. Owing to the worldwide prevalence of hot spot *RET* germline mutations [6], the present study results, in essence, are generalizable to other geographical areas of the earth.

The present findings have important implications for other monogenic disease. Differences between index and non-index patients are greatest for early-onset syndromic manifestations but negligible for late-onset syndromic manifestations. Wider use of population genomic screening may unearth more node-negative and smaller MTCs [15], diminishing disparities between index and non-index patients going forward. Because they exhibited similar age and tumor characteristics for the secondary and tertiary manifestations of MEN2A, screening for these syndromic components remains an integral element of MEN2A management in index and non-index patients alike.

Author contributions AM: conceptualization, methodology, validation, formal analysis, investigation, writing - original draft. KL: investigation, writing - review & editing. FW: investigation, writing - review & editing. TB: investigation, writing - review & editing. DFS: investigation, writing - review & editing. HD: conceptualization, methodology, investigation, writing - review & editing, supervision.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests. To err on the side of transparency, Andreas Machens and Henning Dralle wish to disclose that they served as unpaid members on the American Thyroid Association Guidelines Task Force on Medullary Thyroid Carcinoma which wrote and authored the 2015 Revised American Thyroid Association Guidelines for the Management of Medullary Thyroid Carcinoma (reference #5). The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate Informed consent was obtained from each patient and/or legal guardian as applicable before each *RET* gene test and each operation, all of which represented standard of care.

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