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Characteristics of Primary Hyperparathyroidism in Multiple Endocrine Neoplasia Type 2A

Hülya Hacişahinoğulları[1], Onour Chasan[1], Gamze Bilik Oyman[1], Ümmü Mutlu[1], İsmail Cem Sormaz[2], Gülşah Yenidünya Yalın[1], Nurdan Gül[1], Ayşe Kubat Üzüm[1], Yasemin Giles Şenyürek[2], Özlem Soyluk Selçukbiricik[1]

[1]İstanbul University, İstanbul Faculty of Medicine, Department of Internal Medicine, Division of Endocrinology and Metabolism, İstanbul, Türkiye
[2]İstanbul University, İstanbul Faculty of Medicine, Department of General Surgery, İstanbul, Türkiye

ORCID ID: H.H. 0000-0001-9989-6473; O.C. 0000-0001-5755-3704; G.B.O. 0000-0001-8636-8700; Ü.M. 0000-0002-5259-7326; İ.C.S. 0000-0001-6907-978X; G.Y.Y. 0000-0002-9013-5237; N.G. 0000-0002-1187-944X; A.K.Ü. 0000-0003-0478-1193; Y.G.Ş. 0000-0001-5339-1840; Ö.S.S. 0000-0003-0732-4764

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ABSTRACT

Objective: Multiple endocrine neoplasia type 2A (MEN2A) is an autosomal dominantly inherited tumour syndrome and primary hyperparathyroidism (pHPT) is one of the major components of MEN2A. Our study evaluated the features of MEN2A-related hyperparathyroidism
Material and Methods: Records of 49 patients with MEN2A followed up at Istanbul Faculty of Medicine were retrospectively reviewed.
Results: This study included 25 females and 24 males, and 55% of the patients had *RET* 634 variants. The median follow-up duration was 12 years. Medullary thyroid cancer (MTC) was present in 44 patients, and the mean age at diagnosis was 30.8±14 years. Pheochromocytoma was detected in 61% of patients, and the mean age at diagnosis was 36.4±12.6 years. Twelve patients (F/M=1) had pHPT, and the mean age at diagnosis was 40±15.7 years. The frequency of pHPT was 6% in the ATA moderate-risk category and 33.3% in the high-risk category (*RET* 634 variants). pHPT developed in 3 of 4 patients carrying the *RET* C634R variant. The most common symptoms were nephrolithiasis and osteoporosis, and 67% of patients had normocalcemic pHPT. Selective surgery was performed in 9 patients and subtotal parathyroidectomy in 1 patient. The median follow-up duration after the diagnosis of pHPT was 10.5 years, and persistent disease developed in 1 patient. Recurrent hyperparathyroidism occurred in 1 patient 12 years after the first operation. Five patients developed permanent hypoparathyroidism.
Conclusion: *The RET* mutation at codon 634 is associated with a high frequency of pHPT, usually accompanied by normocalcemia or, less frequently, mild hypercalcemia.
Keywords: Multiple Endocrine Neoplasia type Type 2A, MEN2A, Primary Hyperparathyroidism

INTRODUCTION

Multiple endocrine neoplasia type 2A (MEN2A) is an autosomal dominantly inherited cancer syndrome caused by a pathogenic germline variant in the Rearranged During Transfection (*RET*) proto-oncogene. *The RET* gene encodes a receptor-type tyrosine kinase and plays a role in cell growth, proliferation, and differentiation. Gain-of-function mutations in the *RET* proto-oncogene cause multiple tumours in tissues where *RET* is predominantly expressed, such as C cells of the thyroid gland, adrenal medulla, and enteric autonomic plexus (1). The prevalence of MEN 2A was reported as 13–24 per million (2, 3).

Classical MEN2A is characterised by medullary thyroid carcinoma (MTC), pheochromocytoma, and primary hyperparathyroidism (pHPT). The penetrance of MTC is approximately 100%. The age of development of MTC depends on the specific *RET* mutation (4). Overall, the penetrance of pheochromocytoma is 32%, and its frequency varies between 10% and 50% according to the *RET* mutation. In patients with the *RET* mutations at codon C634, the penetrance is about 50%. MEN2A-related pheochromocytoma usually occurs earlier than sporadic forms; the incidence rate is highest in the 3rd-4th decade (5, 6). The penetrance of pHPT is lower in MEN 2A

Corresponding Author: Hülya Hacışahinoğulları **E-mail:** mercandogru@hotmail.com
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compared with MEN type 1 (MEN1). The prevalence of pHPT varies between 0-35% depending on the *RET* genotype. pHPT typically presents in the fourth decade of life (range, 12 to 70 years) and is asymptomatic in 42% to 84 % of patients (7, 8). The phenotypic expression of pPHT most often occurs in patients with the *RET* mutation at codon 634. pHPT can rarely be the first manifestation of MEN2A (4, 9).

The American Thyroid Association (ATA) guidelines recommend the screening for pHPT in patients with RET mutation to begin by the age of 11 years for patients in the ATA high-risk category and by the age of 16 years for patients in the ATA moderate-risk category (4). Screening for pHPT includes the measurement of albumin-corrected serum calcium or ionised calcium and intact parathyroid hormone (PTH). Multiglandular disease is less frequent in MEN2A than in MEN1. Imaging modalities to localise enlarged parathyroid glands include neck ultrasonography (USG), technetium Tc 99m sestamibi scintigraphy, ^{18}F-fluorocholine positron emission tomography/computed tomography (PET/CT), and 4-dimensional computed tomography (4D-CT) (10).

The criteria for surgical treatment are the same as those for the sporadic form of pHPT. Surgery options for patients with no history of previous neck surgery are as follows: resection of enlarged glands with intraoperative PTH monitoring, subtotal parathyroidectomy (removal of 3+1⁄2 glands), and total parathyroidectomy with heterotopic autotransplantation. The optimal surgical procedure for managing pHPT remains controversial. However, the guidelines recommend subtotal or total parathyroidectomy with autotransplantation if all glands are enlarged. If there is a history of previous neck surgery (for pPHT or MTC), imaging studies should be performed for localisation in patients who are considered for reoperation (4).

Due to the low penetrance of pHPT in MEN2A syndrome, studies examining the characteristics of pHPT are limited. We evaluated the frequency, clinical and laboratory features, treatment modalities, and long-term follow-up outcomes in patients with MEN2A-associated pHPT.

MATERIAL AND METHODS

This retrospective study included patients who were diagnosed with MEN2A and followed up in the Endocrinology and Metabolic Diseases Clinic of Istanbul Faculty of Medicine between 1992 and 2024. Demographic and clinical characteristics, laboratory results, radiological imaging methods, treatment modalities, surgical procedures, and long-term outcomes were reviewed. The data of the subgroup diagnosed with pHPT were evaluated in detail.

The development of hypercalcemia within 6 months after the operation for pHPT was defined as a persistent disease, and the occurrence of hypercalcemia following a normocalcemic interval after 6 months postoperatively was considered as a recurrent disease. The cure was deemed as normalisation of calcium homeostasis for at least six months after surgery.

The study protocol was approved by the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine (Date: 26.07.2024- No: 14). Informed consent was not obtained due to the retrospective design of the study.

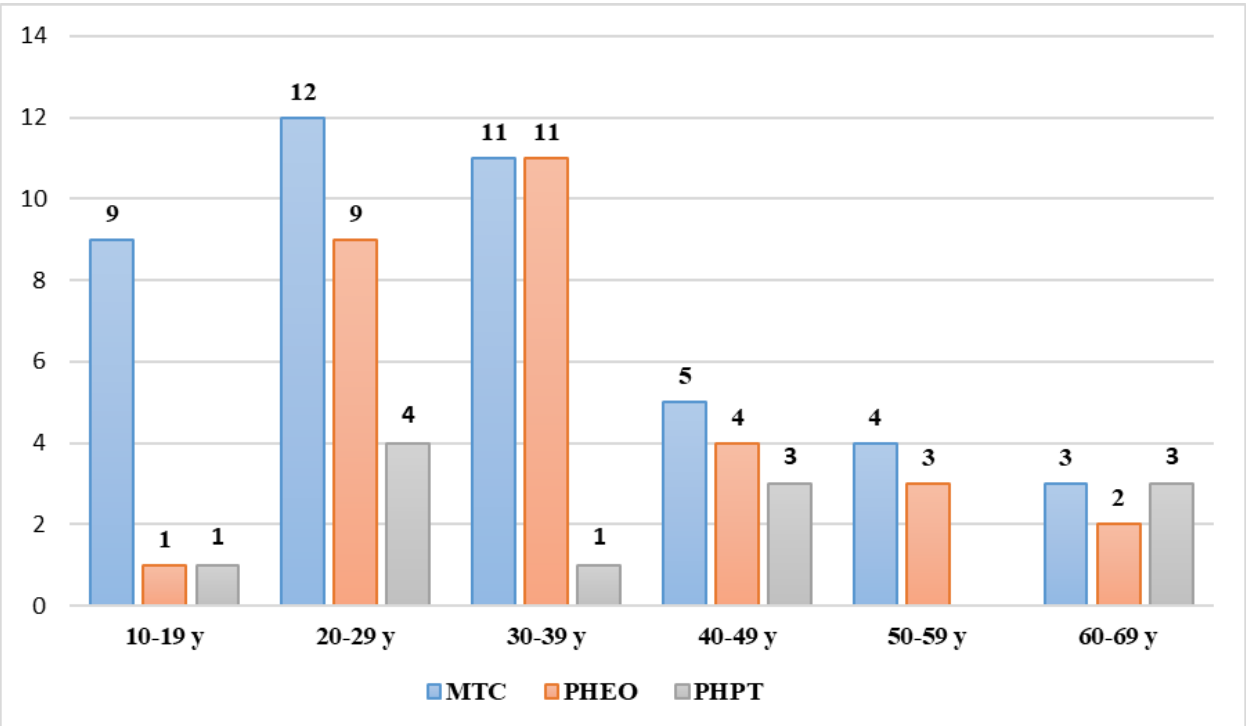

Figure 1: Age-adjusted distributions of the diseases
MTC: Medullary thyroid cancer, PHEO: Pheochromocytoma, PHPT: Primary hyperparathyroidism

Statistical analysis

Statistical analyses were performed using the SPSS software (version 21.0). Categorical variables were presented as the frequency and percentage of occurrence, whereas numerical variables were displayed as the median, mean, and standard deviation (SD).

RESULTS

A total of 49 patients with MEN2A were included in the study, and 25 were female (51%) and 24 were male (49%). The mean age of the patients was 44.8 ± 15 years. The median duration of follow-up was 12 years (range 2 to 36). In 43 of the 49 patients, genetic analysis results were available. The distribution of *RET* variants was as follows: C618A (5/43, 11.5 %), C618R (2/43, 5%), C618S (2/43, 5%), C634A (7/43, 16%), C634G (1/43, 2%), C634R (4/43, 9%), C634S (8/43, 18.5%), C634T (4/43, 9%), C634Y (3/43, 7%), L790F (5/43, 12%), and V804M (2/43, 5%).

All patients underwent total thyroidectomy. Central lymph node dissection was performed in 61% (n=30), and lateral lymph node dissection was performed in 36.7% (n=18) of the patients. Pathological examination was compatible with only C-cell hyperplasia in 5 of the 49 patients and medullary thyroid cancer in the remaining 44 patients. The mean age at diagnosis of MTC was 30.8±14 years (range, 12 to 61) (Figure 1). Sixteen patients underwent multiple surgeries (2 operations in 10 patients, 3 operations in 5 patients, and 4 operations in 1 patient) and 1 patient underwent radiotherapy. Remission was not achieved in 21 patients. Pheochromocytoma was detected in 30 patients (61%). The mean age at diagnosis of pheochromocytoma was 36.4±12.6 years (Figure 1). Bilateral pheochromocytoma was present in 15 patients (50%) at diagnosis. In 3 of 15 patients who underwent unilateral adrenalectomy, pheochromocytoma developed in the other adrenal gland between 7 and 16 years after the first surgery. Recurrence occurred in 4 patients between 5 and 17 years after the first surgery. In 12 patients (11 MTC, 1 patient with C cell hyperplasia), pheochromocytoma was detected before the thyroid operation, and the pheochromocytoma operation was performed primarily followed by the thyroidectomy. In the remaining patients, the interval between the thyroidectomy operation and the diagnosis of pheochromocytoma ranged from 1 to 23 years.

Of the 49 patients, 12 had developed pHPT. The mean age at diagnosis of pHPT was 40±15.7 years (range, 19 to 61) (Figure 1). Seven patients were symptomatic, and the most common symptoms were nephrolithiasis (n=4) and osteoporosis (n=4). Case 12 developed nephrocalcinosis and chronic kidney disease. In 11 patients, the laboratory results at the time of diagnosis were available. The mean albumin-corrected serum calcium level was 10.2±1 mg/dL (normal range 8.5-10.5) and the mean PTH level was 78 pg/ml (normal range 15-65).

USG was performed for preoperative localisation in 10 patients and Tc 99 m sestamibi scintigraphy was performed in 6 of them. Parathyroid lesions were localised in 7 patients. Details are summarised in Table 1. Ten patients underwent parathyroidectomy. One patient did not accept surgical treatment, and parenteral bisphosphonate therapy was applied for osteoporosis. Selective surgery was performed in 9 patients and subtotal parathyroidectomy in 1 patient. The number of excised glands was 1 in 7 patients, 2 in 2 patients and 3+1/2 in 1 patient.

The median follow-up time from pHPT diagnosis to the last follow-up visit was 10.5 years (range 1 to 24). Case 7 developed persistent disease after parathyroidectomy. He has been followed up for 24 years and has not developed an indication for parathyroidectomy. Case 5 developed recurrent hyperparathyroidism 12 years after the first operation. Five patients developed permanent hypoparathyroidism after surgery. Among all patients, permanent hypoparathyroidism developed in 8 patients (8/49), 5 of whom had previous pHPT. In addition, 3 patients without a diagnosis of pHPT developed permanent hypoparathyroidism after thyroidectomy due to MTC.

DISCUSSION

In this study, we retrospectively evaluated 49 patients diagnosed with MEN2A. In particular, we reviewed the clinical and laboratory characteristics, treatment modalities, and long-term outcomes of patients with primary hyperparathyroidism.

In a study conducted in Denmark, it was reported that the female/male ratio was 0.89 and the most common *RET* variant was C611Y (68%) in their study population (3). In our study, the female-to-male ratio was 1.04 and 63% (27/43) of the patients carried the *RET* 634 variant. The ATA guideline categorises the *RET* mutation according to the risk of aggressive MTC. Pathogenic variants at codon 634 are in the high-risk category. While 63% of our patients were in the high-risk category, the remaining 37% were in the moderate-risk category. ATA guidelines recommend thyroidectomy at or before the age of 5 years in children who belong to the ATA high-risk category (4). Kelebwe et al. showed that disease stage and age at diagnosis are independent prognostic factors for medullary thyroid cancer (11). Most of our patients were diagnosed in the 3rd-4th decade and this may be related to the decreased cure rate.

MEN 2A-associated pheochromocytoma usually occurs in the 3rd-4th decade of life. Siqueira et al. reported that the frequency of pheochromocytoma in MEN 2 patients was 31.4% and the mean age at diagnosis was 35.5±13.4 years (12). Similarly, the mean age at diagnosis of pheochromocytoma was 36.4±12.6 years in our study; however, pheochromocytoma was detected more frequently (67%). In the same study, Siqueira et al. also stated that 92.8% of patients with pheochromocytoma had *a RET* mutation at codon 634. In our study, among 30 patients with pheochromocytoma, there were 26 patients for whom genetic results were available. Of these 26 patients, 19 had *a RET* mutation at codon 634 (73%) and the remaining 7 (27%) had *a RET* mutation at codon 618.

Table 1: Characteristics of Patients with PHPT

Patient No	Gender	Age at diagnosis of pHPT (years)	RET Variant	Symptoms	Plasma PTH Levels	Plasma Ca Level*	Neck USG	Treatment Methods	No. of Removed Glands	Age at diagnosis of MTC (years)	Surgical procedures for MTC	Follow up Status
Case 1	M	29	C634R	Osteoporosis	67	9	Right inferior	Medical**		-	TT	
Case 2	F	49	C634R	Osteopenia	225	10.7	Right inferior	Surgery	3+1/2	49	TT+ CLND	HPT
Case 3	F	60	C634S	Osteoporosis	142	10.4	Negative	Surgery	1	60	TT+CLD+LND	Cure
Case 4	M	49	C634Y	-	712	11.7	Right inferior	Surgery	1	50	TT+CLD+LND	Cure
Case 5	F	19	C634Y	-	249	9.5	Negative	Surgery	2 ***	19	TT+ CLND	Recurrence
Case 6	F	24	C634T	-	185	10	Right inferior	Surgery	1	24	TT+CLD+LND	Cure
Case 7	M	26	NA	Nephrolithiasis	NA	NA		Surgery	1	26	TT+ CLND	Persistence
Case 8	F	60	NA	-	87	9.1	Negative	Follow up		32	TT	
Case 9	F	27	C634T	-	74	9	Right	Surgery	2****	28	TT+CLD+LND	HPT
Case 10	M	30	C634R	Nephrolithiasis	106	10.2	-	Surgery	1	30	TT+ CLND	HPT
Case 11	M	61	C618S	Nephrolithiasis Osteoporosis	115	10.4	Negative	Surgery	1	61	TT+CLD+LND	HPT
Case 12	M	45	C634A	Nephrolithiasis Osteoporosis	1172	12.2	Left inferior	Surgery	1	45	TT+ CLND	HPT

*Plasma albumin-corrected Ca Level **Patient was treated with intravenous zoledronic acid *** Right and left inferior ****Right superior and inferior
NA: Not available, PTH: Parathyroid Hormone, PHPT: Primary Hyperparathyroidism, Ca: Calcium, HPT: Hypoparathyroidism, TT: Total Thyroidectomy, TT + CLND: Total thyroidectomy combined with central lymph node dissection, TT + CLD + LND: Total thyroidectomy combined with central lymph node dissection and lateral neck dissection, albumin-corrected serum calcium level normal range: 8.5-10.5mg/dL, PTH normal range:15-65 pg/mL

MEN2A-related hyperparathyroidism is usually asymptomatic. In the study of Holm et al., it was reported that the median age at the time of diagnosis of pHPT was 45 years, 75% of patients were asymptomatic, and the most common symptoms were osteoporosis and polydipsia (13). Unlike this study, 58% (7/12) of the patients were symptomatic and the most common symptoms were nephrolithiasis and osteoporosis in our study, and the median age at diagnosis of pHPT was 37.4 years. In the study by Raue et al. it was shown that serum calcium was slightly elevated in 69% of the patients with pHPT and normal in 16% (8). In our study, among the 12 patients, 67% (8/12) had normocalcemic primary hyperparathyroidism, 17% (2/12) had mild hypercalcemia, and only one patient (1/12) had moderate hypercalcemia. Rau et al. also reported that pHPT and medullary thyroid carcinoma were diagnosed synchronously in 75% of patients (8). Similarly, in our study, pHPT was found concomitantly with MTC in 83% of patients. Pheochromocytoma was also present in 10 (83%) patients with pHPT. *RET* mutation at codon 634 was present in 9 of these 10 patients in our study.

The RET mutation at codon 634 is reported to be associated with the presence of pheochromocytoma and hyperparathyroidism (14). Mulligan et al. showed that patients with *the RET* C634R variant had a higher risk of developing parathyroid disease than the other 634 variants (15). On the other hand, it was reported that pHPT developed in 32% of patients carrying *the RET* C634R variant in German families, which was not as high as previously reported (16). In our study, pHPT developed in 3 of 4 patients carrying *the RET* C634R variant. In the study of Holm et al, it was found that the frequency of pHPT was 5% in the ATA moderate-risk category and 50% in the high-risk category (13). In our study, the frequency of pHPT was 6% in the ATA moderate-risk category and 33.3% in the high-risk category.

In the study by Herfarth et al, the first surgical procedure performed was selective resection in 62% of patients, subtotal resection in 24%, and total parathyroidectomy with autotransplantation in 14%. They found that 8.6% of patients developed persistent hyperparathyroidism and 14.3% developed recurrent hyperparathyroidism (17). In our study, 10 patients were operated for pHPT, and selective surgery was performed in 9 of these patients. One of the 10 patients developed recurrent disease and one patient developed persistent disease. In the study of Holm et al, it was stated that subtotal parathyroidectomy was performed in 69% of patients

(n=9) and selective surgery in 23% (n=3), and permanent hypoparathyroidism occurred in 46% of patients (n= 6) (13). In our study, permanent hypoparathyroidism occurred in 50% (5/10) of the patients.

CONCLUSION

Consistent with previous studies, in our study, *the RET* mutation at codon 634 was associated with an increased frequency of pHPT, especially in the C634R variant. In contrast, the frequency of pHPT was lower in the ATA moderate-risk category. Calcium levels are mildly elevated and may be associated with uniglandular or multiglandular disease.

Ethics Committee Approval: This study was approved by the Ethics Committee of the İstanbul University, İstanbul Faculty of Medicine (Date: 26.07.2024- No: 14).

Informed Consent: Informed consent was not obtained due to the retrospective design of the study.

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