Multiple endocrine neoplasia type 1 in patients with gastroenteropancreatic neuroendocrine tumors: An opportunity for early diagnosis and appropriate management

ELOÁ PEREIRA BRABO[1], ALINE BARBOSA MORAES[2],
BETHÂNIA SOARES DOS SANTOS MARIJUAN CABEZAS[1] and LEONARDO VIEIRA NETO[2]

[1]Oncology Unit and Neuroendocrine Section, Clementino Fraga Filho University Hospital; [2]Department of Internal Medicine, Endocrine Unit, Medical School and Clementino Fraga Filho University Hospital, Federal University of Rio de Janeiro, Rio de Janeiro 21941-913, Brazil

Received October 20, 2019; Accepted April 10, 2020

DOI:10.3892/mco.2020.2074

Abstract. Gastroenteropancreatic neuroendocrine tumors (GEPNET) are rare tumors that may be sporadic or develop as part of multiple endocrine neoplasia type 1 syndrome (MEN1). The aim of the present study was to report the experience of a Brazilian multidisciplinary outpatient neuroendocrine tumor clinic regarding the clinical diagnosis of MEN1 in a cohort of GEPNET patients. Patient data, including clinical characteristics and the lag time from the onset of symptoms to diagnosis of the first tumor, and further lag time until the diagnosis of MEN1, were retrospectively reviewed. Among 44 GEPNET patients, 6 had a clinical diagnosis of MEN1. Primary hyperparathyroidism and GEPNET were present in all patients in the cohort, and pituitary neuroendocrine tumors were present in 33.3%. The median time interval from the onset of initial symptoms to the diagnosis of the first tumor was 42 months (range, 0-204 months). The median time interval between the diagnosis of the first tumor and the diagnosis of MEN1 was 22 months (range, 1-109 months). The prolonged lag time between the onset of initial symptoms and MEN1 diagnosis may result in substantial morbidity and loss of opportune interventions for the patients. Therefore, greater efforts should be made to shorten these times and improve the care of patients with MEN1.

Correspondence to: Professor Leonardo Vieira Neto, Department of Internal Medicine, Endocrine Unit, Medical School and Clementino Fraga Filho University Hospital, Federal University of Rio de Janeiro, 255 Professor Rodolpho Paulo Rocco Street, 9th floor, University City, Rio de Janeiro 21941-913, Brazil
E-mail: netolv@gmail.com

Abbreviations: GEPNET, gastroenteropancreatic neuroendocrine tumors; MEN1, multiple endocrine neoplasia type 1 syndrome; PHPT, primary hyperparathyroidism; PitNET, pituitary neuroendocrine tumor; PNET, pancreatic neuroendocrine tumor; NFPNET, non-functional pancreatic neuroendocrine tumor; BMD, bone mineral density; MRI, magnetic resonance imaging; NET, neuroendocrine tumor

Key words: multiple endocrine neoplasia type 1, gastroenteropancreatic neuroendocrine tumor, delay in diagnosis, primary hyperparathyroidism, pituitary adenoma, pituitary neuroendocrine tumor

Introduction

Multiple endocrine neoplasia type 1 (MEN1) is a rare hereditary disease that predisposes patients to diverse types of endocrine neoplasms/hyperplasias. MEN1 is clinically defined as the presence of at least two out of three neoplasms: Primary hyperparathyroidism (PHPT), gastroenteropancreatic neuroendocrine tumor (GEPNET), and pituitary neuroendocrine tumor (PitNET) (1). PHPT and PitNET, albeit benign disorders, are associated with disabling symptoms and local/systemic complications, whereas GEPNET are malignant tumors, the outcome of which is frequently fatal (2). According to the literature, non-functional pancreatic neuroendocrine tumors (NFPNET) and duodenal gastrinomas are the most common GEPNET in MEN1 (1). Early diagnosis and the size of GEPNET are prognostic factors in patients with MEN1 (2).

In patients with sporadic GEPNET, a diagnostic delay of up to 96 months was recently reported, which may adversely affect the patient outcome (3). Furthermore, in patients with MEN1, the diagnostic delay was reported to be as long as 9.6 years for index cases (4) and up to 3.5 years for family members (5).

The aim of the present study was to report our experience with the clinical characteristics of MEN1 and the lag time between the onset of the earliest symptoms and the initial diagnosis of the first tumor. The time interval between the diagnosis of the first tumor and the clinical diagnosis of MEN1 was also reported. The study population consisted of patients from our multidisciplinary outpatient neuroendocrine tumor clinic at the Clementino Fraga Filho University Hospital, Federal University of Rio de Janeiro.

Patients and methods

Patients. This is a retrospective review of clinical data obtained from all patients who had a clinical diagnosis of

MEN1 after 2014, in accordance with the international MEN1 guidelines, and were followed up at our multidisciplinary outpatient neuroendocrine tumor clinic (1). Some of the patients were previously being followed up by other clinics in the same hospital prior to being referred to our clinic. Written informed consent was obtained from all patients in the study, along with their permission for the review and publication of the disease-related data.

Diagnosis. The tumor diagnosis was pathologically confirmed. Information on the duration of symptoms was extracted from the data files and confirmed by personal interviews with the patients. The date of diagnosis of the first tumor was considered as the date of the histopathological confirmation of the tumor. The date of MEN1 diagnosis was established when the second tumor was histopathologically confirmed. The functional status of the tumors was determined by biochemical investigations and the corresponding clinical manifestations.

Hyperparathyroidism was confirmed by persistently elevated parathyroid hormone and calcium levels. Additional information regarding the presence of nephrolithiasis and bone mineral density (BMD) was also collected.

The presence of a pancreatic neuroendocrine tumor (PNET) was established by magnetic resonance imaging (MRI) or upper gastrointestinal endoscopic ultrasound and was confirmed by histopathological examination. Gastrinomas were diagnosed by taking into account the clinical symptoms, biochemical analysis, endoscopic findings, and histopathology. Similarly, pituitary neuroendocrine tumors (PitNET) were confirmed by clinical symptoms, biochemical analysis and MRI of the sella turcica.

The presence of adrenal tumors was assessed by abdominal imaging and biochemical analysis; lipomas and facial angiofibromas were clinically diagnosed.

Statistical analysis. Measures of central tendency were employed for analysis of continuous variables and descriptive statistics for categorical variables. Time was measured in months.

Results

Patient characteristics. A total of 6 patients with MEN1 were identified among 44 patients with GEPNET (13.6%). The median age at initial diagnosis was 47 years (range, 29-66 years). The median age at MEN1 diagnosis was 53 years (range, 31-66 years). A total of 66.6% of the patients were women, and all patients had PHPT.

Nephrolithiasis was present in 66.6% of the patients, and the same frequency was observed for low BMD. A total of 2 patients suffered from brown bone tumor secondary to PHPT. All patients but 1 were treated with parathyroidectomy.

Among the 6 MEN1 patients with GEPNET, there were 5 patients with gastrinomas, 4 in the duodenum and 1 in the cystic duct (6), and 5 patients with NFPNET; in 4 patients there was a coexistence of duodenal gastrinoma and NFPNET; 3 patients presented with a GEPNET as their first MEN1-related tumor. The treatment consisted of surgery, peptide radionuclide radiotherapy, somatostatin analogues and proton pump inhibitors, either alone, in combination, or sequentially. One

Table I. Clinical characteristics in patients with MEN1.

Case no.	Sex	Symptom duration (months)[a]	Age at first diagnosis (years)	First diagnosis	Time to MEN1 diagnosis (months)	PHPT	NFPNET	PitNET[b]	Gastrinoma[c]	Other NET	Adrenal tumor	Lipomas	Angiofibromas
1	F	204	29	PitNET	25	Yes	Yes	Yes	Yes	No	Yes	No	Yes
2	F	60	32	GEPNET	1	Yes	Yes	No	Yes	No	Yes	Yes	Yes
3	M	2	41	PitNET	32	Yes	Yes	Yes	Yes	No	No	Yes	Yes
4	F	1	55	PHPT	109	Yes	Yes	No	No	No	No	No	No
5	M	24	61	GEPNET	20	Yes	Yes	No	Yes	No	Yes	Yes	Yes
6	F	84	66	GEPNET	9	Yes	No	No	Yes	No	No	No	No

[a]The symptom's duration to the first tumor diagnosed. [b]Case 1: Acromegaly; case 3: Giant prolactinoma. [c]Cases 1, 2, 3 and 5: Duodenal gastrinoma; case 6: Cystic duct gastrinoma. F, female; M, male; GEPNET, gastroenteropancreatic neuroendocrine tumor; PitNET, pituitary neuroendocrine tumor; PHPT, primary hyperparathyreoidism; MEN1, multiple endocrine neoplasia type 1; NET, neuroendocrine tumor; NFPNET, non-functional pancreatic neuroendocrine tumor.

Table II. Management of patients with MEN1.

Case no.	PHPT	NET	PitNET	Other tumors	Outcome
1	Surgery	Distal pancreatectomy	Octreotide LAR 30 mg/month plus pegvisomant 10 mg 3 days per week	Observation[c]	Alive, all diseases controlled
2	Surgery[a]	1˚-Somatuline 120 mg/month 2˚-Lutetium 200 mCi	-	Observation[c]	Alive, relapse of forearm graft site
3	Surgery[b]	Lanreotide 120 mg/month Waiting for lutetium therapy	Cabergoline 0.5 mg/day	-	Alive, progressive PNET and PHPT
4	Surgery	Duodenopancreatectomy	-	-	Alive, all diseases controlled
5	Observation	Duodenopancreatectomy	-	Observation[c]	Alive, all diseases controlled
6	Surgery	Cholecystectomy	-	-	Alive, all diseases controlled

[a]Relapse of forearm graft site. [b]Subtotal parathyroidectomy. [c]Adrenal tumor. PitNET, pituitary neuroendocrine tumor; PHPT, primary hyperparathyroidism; MEN1, multiple endocrine neoplasia type 1; PNET, pancreatic neuroendocrine tumor; NET, neuroendocrine tumor; LAR, long-acting release.

NFPNET patient had metastatic liver disease and another patient had regional portal lymph node metastases.

A total of 2 patients presented with PitNET as their first MEN1-related tumor; one of these 2 patients had acromegaly and the other one had a macroprolactinoma. The patients were treated with surgery plus pegvisomant and cabergoline, respectively. The other patients had no serum or imaging evidence of PitNET.

The distribution of others MEN1 characteristics, such as adrenal tumors, lipomas and facial angiofibromas, is reported in Table I.

Diagnosis. The median time from the onset of initial symptoms to the first tumor diagnosis was 42 months (range, 0-204 months) and the median time from the first tumor diagnosis to MEN1 diagnosis was 22 months (range, 1-109 months) (Table I). The median age at MEN1 diagnosis and the time interval between the initial tumor diagnosis and MEN1 diagnosis both varied depending on the type of initial tumor diagnosis. A patient with an initial diagnosis of PHPT was 64 years old at MEN1 diagnosis, and the time interval from PHPT to MEN1 diagnosis was 57 months. In a group of 3 patients in whom the initial diagnosis was a GEPNET, the median age at MEN1 diagnosis was 63 years (range, 32-66 years) and the time interval between the initial GEPNET diagnosis and MEN1 diagnosis was 9 months (range, 1-20 months). The median age at MEN1 diagnosis for the 2 patients with PitNET was 37 years (range, 31-43 years) and the median lag time from the initial PitNET diagnosis to MEN1 diagnosis was 28.5 months (range, 25-32 months).

The treatment approach and the outcomes of the patients with MEN1 are summarized in Table II. At the time of the last assessment, all 6 patients with MEN1 were alive.

Discussion

This series-based study was undertaken to address the significant delay in the diagnosis of the rare MEN1 syndrome, which results in potential complications, thus causing high morbidity and mortality. Only a limited number of studies in the literature have addressed this issue to date (4,5,7-13). According to the findings of the present study, the median age at the initial diagnosis of the first tumor and at MEN1 diagnosis was markedly high, which is surprising considering the academic nature of our hospital. This may be due to the low level of awareness of this rare disease among physicians, thus leading to the notable delay in diagnosis.

The patients in this study were older when compared to other studies, with a greater female proportion compared with that reported in other studies (4,7-13). However, the higher female proportion observed in the present study should be interpreted with caution, considering the small sample size.

Furthermore, as regards the wide differences observed in the time interval between the initial diagnosis of the first tumor and the MEN1 diagnosis for the different types of first tumors, they must be carefully interpreted. Although the sample size was small, these findings should be further discussed. The longest time interval was observed in the case of a patient who presented with PHPT. In that case, the initial tumor remained undiagnosed for >4 years and, after the diagnosis of PHPT, there was an additional long interval before a MEN1 diagnosis was made. This long delay may be attributed to the non-specific nature of the symptoms, combined with low suspicion of MEN1 among health professionals, particularly with respect to cases with PHPT. Another contributing factor may be the difficulties faced by physicians due to the issues with the public health system in Brazil, ranging from irregular supply of biochemical tests, lack of easy access to nuclear medicine, and inadequate access to good-quality imaging. A shorter time interval was observed when the first tumor diagnosis was a PitNET, possibly because these patients are usually followed by endocrinologists, who are more familiar with MEN1. However, one of our patients who presented with acromegaly remained undiagnosed with primary amenorrhea for 17 years (Table I). The shortest interval was for patients with GEPNET as the

Table III. Literature review of delay in diagnosis of MEN1.

Author (Refs.)	No. of patients	Age at first diagnosis (years)	Age at MEN1 diagnosis (years)	Female sex (%)	Time from symptoms to first diagnosis (years)	Time from first diagnosis to MEN1 (years)	Time from first symptoms to MEN1 (years)	PHPT frequency (%)	GEPNET frequency (%)	PitNET frequency (%)
Yamazaki *et al* (4), Sakurai *et al* (7)	185	40.4±14.4	47.5±13.5	55.4	2-9.6[a]	0.4-4.2[a]	NR	94.4	58.6	49.6
Lourenço *et al* (8,9)	17	NR	46.7±12.34	35.7	20.7±2.58[b]	NR	NR	100	78.6	50
Carty *et al* (10)	17	NR	40.7 (18-86)	55	NR	NR	7.6 (0-29)	76.4	55.8	38.2
Christopoulos *et al* (11)	22	NR	39.8	69	NR	NR	17.2	NR	NR	NR
Pieterman (12)	43	NR	34±14 (11-64)	49	NR	NR	9.5 (1-36)	95	67	49
Vergès *et al* (13)	324	33.9±14.0[d,e] 35.0±14.4[d,f] 41.6±14.0[d,g]	NR	NR	NR	9.0±8.1[d,e] 5.2±5.1[d,f] 4.1±4.0[d,g]	NR	95	54	42
Present study	7	55 (29-67)[c]	62 (31-67)[c]	66.6	5 (0.08-17)	1.66 (0.08-9)	7.80 (34-229)	100	100	28.5

[a]According to different symptoms; [b]nephrolithiasis to PHPT; [c]median; [d]mean; [e]PA as first tumor; [f]PHPT as first tumor; [g]GEPNET as first tumor. NR, not reported; MEN1, multiple endocrine neoplasia type 1; PHPT, primary hyperparathyreoidism; GEPNET, gastroenteropancreatic neuroendocrine tumor; PitNET, pituitary neuroendocrine tumor.

first tumor diagnosis. This may be attributed to the multidisciplinary nature of our team and routine clinical screening of all patients in our outpatient neuroendocrine tumor (NET) clinic.

All 44 patients included in the current study presented with GEPNET, which reflects the study population. The patients were referred after a diagnosis of a NET from any other clinic of our hospital or from other institutions. The frequency of MEN1 among our GEPNET patients was 13.6%, which is consistent with the results from a proposed predicting model from The Netherlands and Sweden (14).

Moreover, the high frequency of PHPT was as expected. Previous Brazilian MEN1 studies have reported similar results (8,9), which are also similar to those observed in studies from Japan (4,7), The Netherlands (12), and France/Belgium (13) (Table III). The high frequency of nephrolithiasis, low BMD, and the high percentage of cases diagnosed in patients aged >50 years (50%) in the present study, reflect the late diagnosis of this disorder and consolidate the natural history of MEN-related PHPT, which has been previously reported (11,15-18).

In this case study, PitNET diagnosis frequency was 33.3%, which is similar to that reported in diverse studies with bigger sample sizes. The frequency of PitNET in MEN1 is greatly variable (4,7-13,19). The frequency observed in the present study must be interpreted with caution due to the small sample size. Furthermore, a longer follow-up is required to re-evaluate this frequency.

The long delay before a diagnosis of MEN1 is established has been previously reported in studies from countries including Brazil (8,9), Japan (4,7), The Netherlands (12), United States (10), Greece (11), and France/Belgium (13). These data are summarized in Table III.

The delay in the diagnosis of an index case may have a serious impact on patient morbidity and prognosis. Undiagnosed PHPT may evolve into a brown tumor and low BMD, with subsequent bone pain and increased risk of fractures. Nephrolithiasis, which is another common manifestation, may cause pain, increased risk of urinary tract infection, and renal dysfunction (15-18).

Prolactinomas and somatotropinomas (acromegaly) are the most common PitNET tumors in the MEN1 context, and they may be associated with visual field defects, cardiovascular morbidity and mortality, notably acromegaly. These manifestations are time-dependent and directly associated with late diagnosis (13). Moreover, prolactinomas may also present with hypogonadism secondary to increased levels of prolactin, which may further impair bone health already compromised by PHPT in MEN1 patients.

In general, due to the rarity of acromegaly and the lack of awareness in the general population as well as healthcare professionals themselves, the diagnosis is frequently made after years of active disease, thus increasing the risk of coexisting complications. These complications are mainly cardiovascular and oncological (20). Therefore, increased awareness of acromegaly amongst healthcare professionals is of utmost importance in order to improve patient outcomes.

Metastatic disease is the most significant factor responsible for poor survival among PNET patients. The risk of metastasis increases in direct association with the size of a PNET tumor (2). In non-functional tumors, even with localized disease, patients may suffer from symptoms due to compression of adjoining

organs secondary to enlarging tumors. In patients with functional PNET, hypersecretion of insulin may be a life-threatening condition, while gastrinoma patients may present with a long history of severe peptic disease that may persist for >7 years (6). The diagnosis of MEN1 is crucial for ensuring appropriate management of PNET and gastrinomas. The prognosis and treatment are different depending on whether the tumor is sporadic or part of a genetic predisposition syndrome, such as MEN1. The surgical treatment of GEPNET as part of MEN1 have particularities regarding the type, timing and extent of the procedures (21).

Another important concern is the delay in the diagnosis of family members. All first-degree relatives of an index case must be screened for MEN1 (1). A Dutch study based on a national database of MEN1 patients reported a long lag time between the index case diagnosis and the diagnosis of family members. The authors reported that, 20% of the GEPNET in family members were metastatic and 10 MEN1-related deaths occurred before diagnosis could be made in 247 family members from 58 families with MEN1. However, the lag time for diagnosis of family members has decreased over the last few decades (22).

The limitations of the present study are the small sample size and the retrospective design. The aim was to highlight the lag time for MEN1 diagnosis and the resultant substantial morbidity in these patients. We hope this can alert the physicians involved in the care of GEPNET patients of the possibility of MEN1. Another limitation of the present study is the lack of genetic confirmation. Genetic tests are not easily available in the Brazilian public health system (23). However, some Brazilian cohort studies have reportedly utilized genetic testing, initially performed by Sanger sequencing (8,9,17,24-26) and, more recently, by multiplex ligation-dependent probe amplification and Sanger sequencing and/or next-generation sequencing (NGS). This is certainly a positive change in the situation in the last decade in Brazil (27,28). However, genetic evaluation of these patients along with screening of their first-degree relatives are currently conducted. Efforts are also made to raise awareness with regard to NET and MEN1 in the medical community through teaching, discussion, and practical skills training.

In conclusion, the diagnostic delay is largely physician-dependent, since these patients usually seek medical assistance for years before diagnosis. Physicians involved in the care of GEPNET patients should be aware of the possibility of MEN1. In addition, they should be prepared for screening and making appropriate treatment available to the patients as well as their first-degree relatives. This may help towards shorter delay in diagnosis, prevention of morbidity, timely appropriate management, and improved prognosis.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

EPB and LVN designed the study, revised the manuscript contents, and maintained the integrity of the data analysis. EPB, ABM and LVN made the drafting of the manuscript. All the authors (EPB, LVN ABM and BSDSMC) conducted the study, reviewed the literature, performed the data collection, data analysis, and the data interpretation, and they have read and approved the final version of the manuscript for publication.

Ethics approval and consent to participate

Written informed consent was obtained from patients prior to enrollment.

Patient consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

Authors' information

EPB obtained a medical degree in 1989. Finished hematology/oncology training in 1996. Member of the medical staff of the Oncology Service of the Federal University of Rio de Janeiro (UFRJ) since 1997. Obtained a Master of Science degree in 2006. Involved in training students and fellows, as well as working as attending physician, mainly for lung cancer and NET patients. She was head of the Oncology Unit at Clementino Fraga Filho University Hospital (2002-2008 and 2017-2019). Member of ASCO, IASLC and ENETS.

ABM is Assistant Professor of Internal Medicine at the Medical School of the UFRJ. She obtained a medical degree in 2004 and finished the Specialization in Endocrinology in 2006. Her Master's degree was in neuroendocrine tumors, specifically pituitary neuroendocrine tumors (2009), and her PhD degree was in adrenal diseases, emphasized in adrenal incidentaloma (2019), both at the UFRJ. Member of the Brazilian Society of Endocrinology and Metabolism.

BSSMC is in the second year of Medical Residency in Oncology at the UFRJ. Obtained a medical degree in 2015 and completed a fellowship in internal medicine in 2017. Attending fellow of the Multidisciplinary Outpatient Neuroendocrine Tumor Clinic at the UFRJ.

LVN is Professor of Endocrinology at the Medical School of the UFRJ. He graduated in 2001 and finished the Medical Residency in Internal Medicine and Endocrinology at the Clementino Fraga Filho University Hospital of the UFRJ in 2005. Obtained Master's and PhD degrees in neuroendocrine tumors (pituitary neuroendocrine tumors), both at the UFRJ. Has published more than 80 articles in internationally recognized scientific journals. The major lines of research currently led by him include adrenal diseases and neuroendocrine tumors, and he has received grants from the state and federal government for his work in the field of science. Member of the Brazilian Society of Endocrinology and Metabolism and Endocrine Society.

References

1. Thakker RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, Melmed S, Sakurai A, Tonelli F and Brandi ML; Endocrine Society: Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab 97: 2990-3011, 2012.
2. Ito T, Igarashi H, Uehara H, Berna MJ and Jensen RT: Causes of death and prognostic factors in multiple endocrine neoplasia type 1: A prospective study. comparison of 106 MEN1/Zollinger-Ellison syndrome patients with 1613 literature MEN1 patients with or without pancreatic endocrine tumors. Medicine (Baltimore) 92: 135-181, 2013.
3. Basuroy R, Bouvier C, Ramage JK, Sissons M, Kent A and Srirajaskanthan R: Presenting symptoms and delay in diagnosis of gastrointestinal and pancreatic neuroendocrine tumours. Neuroendocrinology 107: 42-49, 2018.
4. Yamazaki M, Suzuki S, Kosugi S, Okamoto T, Uchino S, Miya A, Imai T, Kaji H, Komoto I, Miura D, *et al*: Delay in the diagnosis of multiple endocrine neoplasia type 1: Typical symptoms are frequently overlooked. Endocr J 59: 797-807, 2012.
5. De Laat JM, van Leeuwaarde RS and Valk GD: The importance of an early and accurate MEN1 diagnosis. Front Endocrinol (Lausanne) 9: 533, 2018.
6. Moraes AB, Treistman N, Studart MC, Chagas VLA, Brabo EP and Vieira Neto L: Gastrinoma of cystic duct: A rare association with multiple endocrine neoplasia type 1. J Clin Med Res 10: 843-847, 2018.
7. Sakurai A, Suzuki S, Kosugi S, Okamoto T, Uchino S, Miya A, Imai T, Kaji H, Komoto I, Miura D, *et al*: Multiple endocrine neoplasia type 1 in Japan: Establishment and analysis of a multicentre database. Clin Endocrinol (Oxf) 76: 533-539, 2012.
8. Lourenço DM Jr, Toledo RA, Coutinho FL, Margarido LC, Siqueira SA, dos Santos MA, Montenegro FL, Machado MC and Toledo SP: The impact of clinical and genetic screenings on the management of the multiple endocrine neoplasia type 1. Clinics (Sao Paulo) 62: 465-476, 2007.
9. Lourenço DM Jr, Toledo RA, Mackowiak II, Coutinho FL, Cavalcanti MG, Correia-Deur JE, Montenegro F, Siqueira SA, Margarido LC, Machado MC and Toledo SP: Multiple endocrine neoplasia type 1 in Brazil: MEN1 founding mutation, clinical features, and bone mineral density profile. Eur J Endocrinol 159: 259-274, 2008.
10. Carty SE, Helm AK, Amico JA, Clarke MR, Foley TP, Watson CG and Mulvihill JJ: The variable penetrance and spectrum of manifestations of multiple endocrine neoplasia type 1. Surgery 124: 1106-1113, 1998.
11. Christopoulos C, Antoniou N, Thempeyioti A, Calender A and Economopoulos P: Familial multiple endocrine neoplasia type I: The urologist is first on the scene. BJU Int 96: 884-887, 2005.
12. Pieterman CR, Schreinemakers JM, Koppeschaar HP, Vriens MR, Rinkes IH, Zonnenberg BA, van der Luijt RB and Valk GD: Multiple endocrine neoplasia type 1 (MEN1): Its manifestations and effect of genetic screening on clinical outcome. Clin Endocrinol (Oxf) 70: 575-581, 2009.
13. Vergès B, Boureille F, Goudet P, Murat A, Beckeres A, Sassolas G, Goudard P, Chambe B, Montvernay C and Calender A: Pituitary disease in MEN type 1 (MEN1): Data from the france-belgium MEN1 multicenter study. J Clin Endocrinol Metabol 87: 457-465, 2002.
14. de Laat JM, Tham E, Pieterman CR, Vriens MR, Dorresteijn JA, Bots ML, Nordenskjöld M, van der Luijt RB and Valk GD: Predicting the risk of multiple endocrine neoplasia type 1 for patients with commonly occurring endocrine tumors. Eur J Endocrinol 167: 181-87, 2012.
15. Burgess JR, David R, Parameswaran V, Greenaway TM and Shepherd JJ: The outcome of subtotal parathyroidectomy for the treatment of hyperparathyroidism in multiple endocrine neoplasia type 1. Arch Surg 133: 126-129, 1998.
16. Eller-Vainicher C, Chiodini I, Battista C, Viti R, Mascia ML, Massironi S, Peracchi M, D'Agruma L, Minisola S, Corbetta S, *et al*: Sporadic and MEN1-related primary hyperparathyroidism: Differences in clinical expression and severity. J Bone Miner Res 24: 1404-1410, 2009.
17. Lourenço DM Jr, Coutinho FL, Toledo RA, Montenegro FL, Correia-Deur JE and Toledo SP: Early-onset, progressive, frequent, extensive, and severe bone mineral and renal complications in multiple endocrine neoplasia type 1-associated primary hyperparathyroidism. J Bone Miner Res 25: 2382-2391, 2010.
18. Lourenço DM Jr, Coutinho FL, Toledo RA, Gonçalves TD, Montenegro FL and Toledo SP: Biochemical, bone and renal patterns in hyperparathyroidism associated with multiple endocrine neoplasia type 1. Clinics (Sao Paulo) 67(Suppl 1): S99-S108, 2012.
19. Giusti F, Cianferotti L, Boaretto F, Cetani F, Cioppi F, Colao A, Davì MV, Faggiano A, Fanciulli G, Ferolla P, *et al*: Multiple endocrine neoplasia syndrome type 1: Institution, management, and data analysis of a nationwide multicenter patient database. Endocrine 58: 349-359, 2017.
20. Reid TJ, Post KD, Bruce JN, Nabi Kanibir M, Reyes-Vidal CM and Freda PU: Features at diagnosis of 324 patients with acromegaly did not change from 1981 to 2006: Acromegaly remains under-recognized and under-diagnosed. Clin Endocrinol (Oxf) 72: 203-208, 2010.
21. Tonelli F, Fratini G, Falchetti A, Nesi G and Brandi ML: Surgery for gastroenteropancreatic tumours in multiple endocrine neoplasia type 1: Review and personal experience. J Intern Med 257: 38-49, 2005.
22. van Leeuwaarde RS, van Nesselrooij BP, Hermus AR, Dekkers OM, de Herder WW, van der Horst-Schrivers AN, Drent ML, Bisschop PH, Havekes B, Vriens MR, *et al*: Impact of delay in diagnosis in outcomes in MEN1: Results from the dutch MEN1 study group. J Clin Endocrinol Metab 101: 1159-1165, 2016.
23. Toledo RA, Sekiya T, Longuini VC, Coutinho FL, Lourenço DM Jr and Toledo SP: Narrowing the gap of personalized medicine in emerging countries: The case of multiple endocrine neoplasias in Brazil. Clinics (Sao Paulo) 67(Suppl 1): S3-S6, 2012.
24. Toledo RA, Lourenço DM Jr, Coutinho FL, Quedas E, Mackowiack I, Machado MC, Montenegro F, Cunha-Neto MB, Liberman B, Pereira MA, *et al*: Novel MEN1 germline mutations in Brazilian families with multiple endocrine neoplasia type 1. Clin Endocrinol (Oxf) 67: 377-384, 2007.
25. Coutinho FL, Lourenço DM Jr, Toledo RA, Montenegro FL, Correia-Deur JE and Toledo SP: Bone mineral density analysis in patients with primary hyperparathyroidism associated with multiple endocrine neoplasia type 1 after total parathyroidectomy. Clin Endocrinol (Oxf) 72: 462-468, 2010.
26. Dantas NCB, Soares CEL, Martins MRA, Lourenço DM Jr and Quidute ARP: Giant prolactinoma causing hydrocephalus and intracranial hypertension as first manifestations of multiple endocrine neoplasia type 1. Front Endocrinol (Lausanne) 10: 582, 2019.
27. Montenegro FLM, Brescia MDG, Lourenço DM Jr, Arap SS, d'Alessandro AF, de Britto E Silva Filho G and Toledo SPA: Could the less-than subtotal parathyroidectomy be an option for treating young patients with multiple endocrine neoplasia type 1-related hyperparathyroidism? Front Endocrinol (Lausanne) 10: 123, 2019.
28. Carvalho RA, Urtremari B, Jorge AAL, Santana LS, Quedas EPS, Sekiya T, Longuini VC, Montenegro FLM, Lerario AM, Toledo SPA, *et al*: Germline mutation landscape of multiple endocrine neoplasia type 1 using full gene next-generation sequencing. Eur J Endocrinol 179: 391-407, 2018.