Endocrine (2023) 82:480–490
https://doi.org/10.1007/s12020-023-03497-2

REVIEW

Multiple endocrine neoplasia type 4 (MEN4): a thorough update on the latest and least known men syndrome

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Received: 27 July 2023 / Accepted: 14 August 2023 / Published online: 26 August 2023

Abstract

Purpose Multiple endocrine neoplasia type 4 (MEN4) is a rare multiglandular endocrine neoplasia syndrome, associated with a wide tumor spectrum but hallmarked by primary hyperparathyroidism, which represents the most common clinical feature, followed by pituitary (functional and non-functional) adenomas, and neuroendocrine tumors. MEN4 clinically overlaps MEN type 1 (MEN1) but differs from it for milder clinical features and an older patient's age at onset. The underlying mutated gene, *CDKN1B*, encodes the cell cycle regulator p27, implicated in cellular proliferation, motility and apoptosis. Given the paucity of MEN4 cases described in the literature, possible genotype–phenotype correlations have not been thoroughly assessed, and specific clinical recommendations are lacking. The present review provides an extensive overview of molecular genetics and clinical features of MEN4, with the aim of contributing to delineate peculiar strategies for clinical management, screening and follow-up of the last and least known MEN syndrome.

Methods A literature search was performed through online databases like MEDLINE and Scopus.

Conclusions MEN4 is much less common that MEN1, tend to present later in life with a more indolent course, although involving the same primary organs as MEN1. As a consequence, MEN4 patients might need specific diagnostic and therapeutic approaches and a different strategy for screening and follow-up. Further studies are needed to assess the real oncological risk of MEN4 carriers, and to establish a standardized screening protocol. Furthermore, a deeper understanding of molecular genetics of MEN4 is needed in order to explore p27 as a novel therapeutic target.

Keywords Neuroendocrine neoplasms · MEN4 · CDKN1B · Hyperparathyroidism · Neuroendocrine tumor · Pituitary adenoma

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Introduction

Multiple endocrine neoplasia (MEN) syndromes are rare autosomal dominant disorders with high penetrance that lead to the development of hyperplasia and/or tumors in at least two endocrine glands in affected individuals. Two MEN syndromes have long been known and are well characterized: the MEN type 1 (MEN1) and type 2 (MEN2). The most frequent one is the MEN1 syndrome, which is characterized by primary hyperparathyroidism (PHPT) due to parathyroid hyperplasia/adenomas, functional or non-functional pancreatic neuroendocrine tumors (NETs) and pituitary adenomas (PitAds). Besides these classical endocrine diseases, in recent years, a great variety of clinical manifestations have been associated with MEN1 so that more than twenty endocrine and non-endocrine tumors have been included in the clinical spectrum of the disease [1]. MEN1 is caused by germline heterozygous loss-of-function mutations in the tumor suppressor gene *MEN1*, located on chromosome 11q13, and encoding the protein menin. Mutations in the *MEN1* gene are broadly distributed throughout its nine protein-coding exons, and cause loss of function of the menin protein. Notably, approximately 10–30% of patients with familial or sporadic MEN1-like phenotypes do not have *MEN1* mutations or deletions [1].

MEN2, a less common condition, is caused by germline gain-of-function mutations in the *RET* proto-oncogene and is characterized by medullary thyroid carcinoma, pheochromocytoma (PHEO) and PHPT. MEN2 is further divided into MEN2A that typically manifests with medullary thyroid cancer, PHEO, and PHPT, and MEN2B that manifests with MEN2A features, although typically lacking PHTP, ganglioneuromas of the lips, tongue and colon, and a marfanoid habitus [2].

In 2002 a novel MEN syndrome, that shares phenotypic features with both MEN1 and MEN2 syndromes, was discovered in rats and was called MENX. Specifically, these rats presented with multifocal anterior PitAd and bilateral adrenal PHEO, as well as extra-adrenal paragangliomas, thyroid C-cell hyperplasia, parathyroid hyperplasia, and pancreatic islet cells hyperplasia. Linkage analysis allowed to identify the gene responsible for the MENX syndrome: the *CDKN1B* gene encoding the cell cycle inhibitor p27 [3]. Following the identification of the pathogenetic variant of the *CDKN1B* causing the MENX syndrome in rats, the same authors investigated whether mutations in the human homolog *CDKN1B* could explain some of the MEN1-like cases without mutations in *MEN1* and identified a germline heterozygous nonsense mutation at codon 76 in a female proband with growth hormone (GH)-secreting PitAd and PHPT [4]. In the following years, other authors, analyzing a series of suspected MEN1 patients, previously tested negative for germline *MEN1* mutations, identified a germline *CDKN1B*/p27 mutation (a 19-bp duplication in exon 1) in a second patient with PitAd, carcinoid tumor and PHPT [5]. Subsequently, a novel MEN syndrome was recognized and submitted to the Online Mendelian Inheritance in Man database in 2007 under the name of MEN4.

MEN4 has an estimated prevalence of less than one per million with less than 80 cases reported so far in the literature [6]. As recently reported, the clinical penetrance and precise tumor spectrum of MEN4 are still poorly defined. Therefore, the establishment of evidence-based management guidelines remains difficult [7].

This narrative review provides an extensive overview of genetics and clinical features of MEN4, in comparison with the MEN1 syndrome, with the aim of contributing to delineate peculiar strategies for clinical management, screening and follow-up of the last and least known MEN syndrome.

Methods

The pertinent literature was carefully revised employing online databases like MEDLINE and Scopus database. On these websites, we searched for articles using key terms related to MEN type 4. The MeSH terms "MENs", "neuroendocrine neoplasms", "MEN4", "*CDKN1B*/p27", "hyperparathyroidism", "pituitary adenoma" were used. We included in the present paper only the articles matching the following inclusion criteria: English language and publication in peer-reviewed journals. We excluded articles for irrelevance to the topic in question, duplicates, and papers written in other languages apart from English.

Insights into the genetics of MEN4

CDKN1B gene function, related pathways and mutations

CDKN1B codes for p27Kip1 (hereafter referred to as p27), a cyclin-dependent kinase inhibitor (CKI) that acts as a tumor-suppressor. Its main substrate is cyclin D, that p27 can bind when it is alone or when complexed to its catalytic cyclin-dependent kinase (Cdk) subunit Cdk4 [8]. When bound to p27, Cdk4 is unable to phosphorylate the retinoblastoma protein (Rb), which then remains bound to E2F transcription factors and consequently the cell cycle is arrested in the G1 phase. Moreover, p27 binds and inhibits other cyclin/Cdk complexes, like Cyclin E/Cdk2 and Cyclin A/Cdk2, stopping the cycle even in S phase (Fig. 1). For this reason, p27, together with p21 (*CDKN1A*) and p57 (*CDKN1C*), members of the same family of cell cycle inhibitors (the CIP/KIP family), controls the beginning and the progression of the cell cycle. These three CKIs share a region of high homology at their N-terminal portion, that contains binding domains to cyclin/Cdk complexes [9]. Beyond this canonic function of

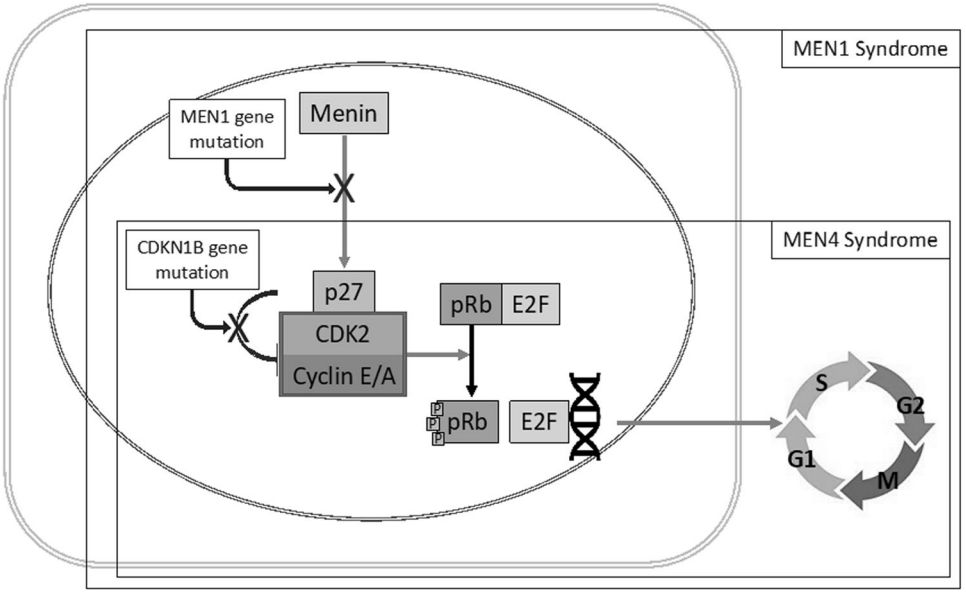

Fig. 1 Exemplification of the aberrant regulation/expression of signaling pathways downstream the mutated genes in MEN1 (MEN1 gene) and MEN4 (CDKN1B gene) syndromes

p27, additional roles have been described, depending on the cellular compartment. In the cell nucleus, p27 inhibits the cell cycle progression but also promotes the differentiation of embryonic stem cells and is a pivotal factor to stop *SOX-2* transcription in induced pluripotent stem cells (iPSCs) [10]. On the other side, when p27 is in the cytoplasm, it interacts with stathmin, a protein that stimulate depolymerization of microtubules, through its C-terminal portion. Thus, p27 has a role in regulating cellular migration and mitotic spindle stability [11–13]. The C-terminus of p27 is not shared with other CIP/KIP family members, and is characterized by an intrinsically disordered region, that allows p27 to assume different tertiary structures through which it is able to interact with multiple substrates [14]. Moreover, in the cytoplasm of amino acid-deprived cells, p27 promotes autophagy through a mammalian target of rapamycin (mTOR)-dependent pathway [15]. Because of this great variety of functions, p27 mutations are deemed to act as driver factors in several tumors [16, 17]. Noteworthy, they seem to occur frequently in hormone-related tumors, such as luminal breast cancer, prostate cancer, small intestine NET and pituitary tumors [18–21]. In sporadic tumors *CDKN1B* mutations are mostly located in the protein coding sequence, while *CDKN1B* germline variants could involve even untranslated regions (UTRs). Interestingly, these pathogenetic variants often translate in truncated forms of p27 protein, that lack the C-terminal region, suggesting a pivotal role of "unconventional" p27 pathways in carcinogenesis [6, 22].

Epigenetic regulation of tumorigenesis

Molecular advances support the contribution of epigenetics in the tumorigenesis of MEN4, in particular regarding the modulation of *CDKN1B* expression by menin. By binding to the mixed-lineage leukemia (MLL) family of proteins, menin becomes part of a complex with histone methyltransferase (HMT) activity, which regulates gene transcription [23]. Specifically, the interaction of menin-MLL-HMT complex with the regulatory elements of the *CDKN1B* promoter regions promotes histone methylation and gene transcription, which lead to increased p27 expression and inhibition of cell cycle progression and cell proliferation [23–26]. There is evidence in literature that menin loss of function and/or MLL inactivation are directly associate to p27 down-regulation: Borsari et al. showed that the biallelic inactivation of *MEN1* leads to inhibition of *CDKN1B* transcription and decreased p27 expression [26]. A strong reduction of p27 levels is observed upon *CDKN1B* mutations occurring either alone or associated with *MEN1* aberrations as a second germline hit [27]. The functional role of the interaction among menin, MLL and p27 is additionally supported by the decreased p27 levels in parathyroid and pancreatic MEN1-related neoplasms [28]. Further investigations are warranted to explore the role of the epigenetic alterations whether as disease drivers or direct consequences of the tumorigenesis process, with the aim to contribute to a deeper understanding of MEN4 pathogenesis and to identify potential molecular targets for epigenetic therapeutic strategies in these patients.

The impact of genotype on phenotype

The possibility to predict phenotype from a specific genotype is of extreme importance in management of MEN affected patients, that may suffer from a wide and variable spectrum of endocrine and non-endocrine disorders, and

may guide an individualized clinical management and follow-up. To establish a genotype-phenotype relation, a large number of different mutations in the same gene with a complete phenotypic characterization is necessary. In patients with MEN1, that is more frequent than MEN4 (3–20/100.000 inhabitants with MEN4 represent 1.5–3.7% of them) [5, 29, 30], a possible genotype-phenotype correlation has been excluded based on intra-familiar variability in type and severity of manifestations [31, 32], while a clear correlation between RET pathogenic variants and MEN2 phenotype has been reported [33]. Only in one study that considered 188 MEN1 patients it has been suggested that pathogenetic variants of *MEN1* in exon 2 could be related to an increased prevalence of gastroenteropancreatic NETs (GEP-NETs), either with an increased risk of metastasis [34]. On the contrary, a genotype-phenotype correlation has been well established in MEN2, although several pathogenic variants of the RET gene, located on chromosome 10q11.2, have been described in the literature to date [35].

Despite the limited number of cases reported in the literature, a recent review of 74 MEN4 cases suggested that pathogenic variants at codons 94–96 of p27 gene may represent a risk of developing PHPT and PitAds over time (log-rank test, $P < 0.001$ and $P = 0.031$, respectively), but not for developing NET [6]. These codons codify for amino acids that are located near the domains responsible for the interaction of p27 with CDKs and Cyclins to control cell cycle, and this could explain the higher risk to develop a neoplasia, but once again it doesn't explain the tissue selectiveness of the syndrome [36]. Moreover, it was noted that pathogenic insertions/deletions in *CDKN1B* are characterized by a higher risk of developing PHPT when compared with missense variants (24/36 vs 11/28, $p = 0.029$) [6].

MEN1 phenocopies: how many cases are explained by MEN4?

Approximately 5–30% of patients with MEN1-like disease, i.e., showing tumors in as few as 1 of the 3 main MEN1-associated endocrine tissues, may not have mutations in the menin coding region: these patients are named phenocopies. It has been postulated that some of these cases can be caused by mutations in the promoter or in UTRs of the *MEN1* [31, 37, 38]. In one study, targeted next-generation sequencing (NGS) of the entire genomic region of *MEN1* was performed to investigate germline mutations in 76 unrelated MEN1 probands. Different pathogenic or likely pathogenic variants were identified in the coding region and splicing sites of the gene in 60 of 76 patients, while no mutation was detected in 16 of 76 patients. However, none of the 76 cases had mutation in noncoding regions of *MEN1*, suggesting that they may be very rare [39]. Other phenocopies may rarely test positive for germline mutations in genes associated to MEN1-like phenotypes (e.g., *CDKN1B* or other *CDKI* genes, *CDC73, CASR, GNA11, AP2S1, GCM2*, and *AIP*) [40–42]. *CDKN1B* mutations could explain just 1–3.5% of them, but often all genetic tests of first and second levels are negative [29]. Phenocopies are not so rare and therefore they represent an important clinical challenge: is it necessary to exclude the presence of other MEN-associated neoplasia? What timing of follow up should be propose? Is it necessary to screen first-degree relatives for the syndrome manifestations? If yes, how old should the patient be to start the screening and what should be the first clinical assessment to carry on?

It should be considered that phenocopies have been described in up to 5–10% of MEN1 kindred [41, 43, 44]. Of note, genetic analysis of a large MEN1 family cohort consisting of 152 members indicated that 10% of individuals within the family who were diagnosed as being affected by MEN1, following familiar (1 first degree relative plus 1 out of 3 MEN1 typical neoplasia) or clinical (2 out of 3 MEN-1 typical neoplasia) criteria, did not harbor a *MEN1* mutation [45]. Thus, a negative genetic test of a family member does not exclude positivity of another member with an MEN1-like clinical condition.

A possible explanation for phenocopies could be found in epigenetic variation. The improvement in genomic and proteomic techniques allowed to demonstrate that abnormal expression of non-coding-RNAs known to be involved in the regulation of menin expression, may explain defects in the protein's function without identified *MEN1* pathogenetic variants [46]. In particular, in a study where the levels of microRNAs were compared between parathyroid adenomas with or without *MEN1* loss-of-heterozygosity (LOH), an increased expression of miR-1301 was suggested to suppress expression of *CDKN1B* in the subgroup positive for *MEN1* LOH [47]. This finding supports the hypothesis that *CDKN1B* inhibition could have a pivotal role in developing a MEN phenotype.

Spectrum of disorders

A German family where PitAds, PHPT, renal angiomyolipomas and testicular cancers were present in various members carrying a *CDKN1B* mutation was the first documented occurrence of a syndromic presentation of the disease later termed MEN4 [4]. Soon thereafter, a germline heterozygous variant of *CDKN1B* was reported in another MEN1 phenocopy, a Dutch female patient presenting with small cell carcinoma of the cervix, ACTH-secreting PitAd, and PHPT [5]. Considering these examples, it seems that MEN4 is associated with other neoplasms in addition to those typically seen in MEN1 but, due to the small number of reported cases, it is still unclear whether these represent distinctive clinical features of this syndrome [17, 48, 49].

Table 1 Spectrum of disorders in MEN 4 syndrome: clinical features, diagnosis and therapy

	Frequency	Markers	Clinical manifestations	Diagnosis	Therapy
PHPT	>90%	PTH, Calcium	Fatigue	Ultrasonography	Surgery
			Renal stones	CT	
			Osteoporosis Gastrointestinal/ Neuropsychiatric symptoms	Technetium-99 m-sestamibi-scintigraphy	
PitAd	25%	IGF1	Asymptomatic	MRI	Surgery
	(NF 10%, acromegaly 7–10%, Cushing disease 5–7%, prolactinomas rare)	Cortisol secretory status (24-h urinary free cortisol, overnight 1-mg dexamethasone suppression test, night salivary cortisol)	Visual field defects		Medical therapy (SSAs, pegvisomant, cabergoline
		PRL	Acromegaly or Cushing disease relative symptoms		-acromegaly-ketoconazole mifepristone, pasireotide
					-Cushing disease-)
					RT
GEP-NETs	<20%	Gastrin Chromogranin A Pancreatic polypeptide	Asymptomatic	Ultrasonography	Surgery
		Vasointestinal polypeptide	Compressive symptoms	CT	Medical therapy (SSAs)
		Glucagon	Hormone hypersecretion syndromes	MRI	PRRT
		Insulin		^{68}Ga-DOTATOC PET/CT	TKI
					CHT

PHPT primary hyperparathyroidism, *PitAd* pituitary adenoma, *NF* non-functioning, *GEP-NET* gastroenteropancreatic neuroendocrine tumors (mainly, duodenopancreatic NET), *SSA* somatostatin analogs, *PRRT* peptide receptor radionuclide therapy, *TKI* tyrosine kinase inhibitors

Pre-clinical studies on MENX rats proved that *CDKN1B* loss causes different neoplasms with very high penetrance. In this model, tumors tend to develop in this chronological order: PHEO, PitAd, medullary thyroid carcinoma, parathyroid adenoma, pancreatic hyperplasia [4, 30]. Similar to the situation in MENX rats, where the *CDKN1B* pathogenetic variant is associated with the predisposition to develop multiple NETs in different organs, also MEN4 patients can present with a variety of tumors and as such they should be followed-up by a multidisciplinary team of expert.

The wide spectrum of disorders in MEN4 syndrome is summarized in Table 1 and Fig. 2.

PHPT is the most common (>90% of cases) and often the first manifestation of MEN4. Mean age at diagnosis of PHPT is in the fifth decade, older than for MEN1 patients [50, 51]. The youngest MEN4 patient presenting with PHPT was 14 years old, while for MEN1 it was 8 years old [52, 53]. PitAds occur in about 40% of MEN4 patients (non-functioning adenomas in 10%, acromegaly in 7–10%, Cushing disease in 5–7%; only one case of prolactinoma reported in the literature). PitAds may affect subjects of all ages: the mean age at onset is 33–35 years, although the youngest case reported was a 5-year-old girl. Although the prevalence of PitAds is quite similar among the two syndromes (40% in MEN4 vs 45% in MEN1), some differences emerge: in MEN1 patients, prolactinomas represent the most common histotype (65% of cases), whereas ACTH-secreting PitAds, which represent only the 5% of cases in MEN1, account for almost 40% of all PitAds in MEN4 patients [54, 55]. In a recent article, a single case of prolactinoma was reported in a patient with a variant of *CDKN1B* [56]. NETs occur in about 20% of MEN4 patients and in 50% of MEN1 patients, and the most frequent primary sites are pancreas, small intestine, and lung [50]. The mean age is 55 years, the youngest case being reported at 34 years in MEN4 [50]. GEP-NETs develop in less than 20% of MEN4 patients, as opposed to a frequency of 55–70% in MEN1 [57, 58]. In MEN4, the most common form of functioning NET is gastrinoma, as in MEN1, while no cases of VIPomas, glucagonomas, insulinomas, or somatostatinomas have been reported so far [50].

Genetic testing for CDKN1B mutations and clinical recommendations

All patients with a clinical evidence of a MEN syndrome should be tested for pathogenetic variants of *MEN1* and

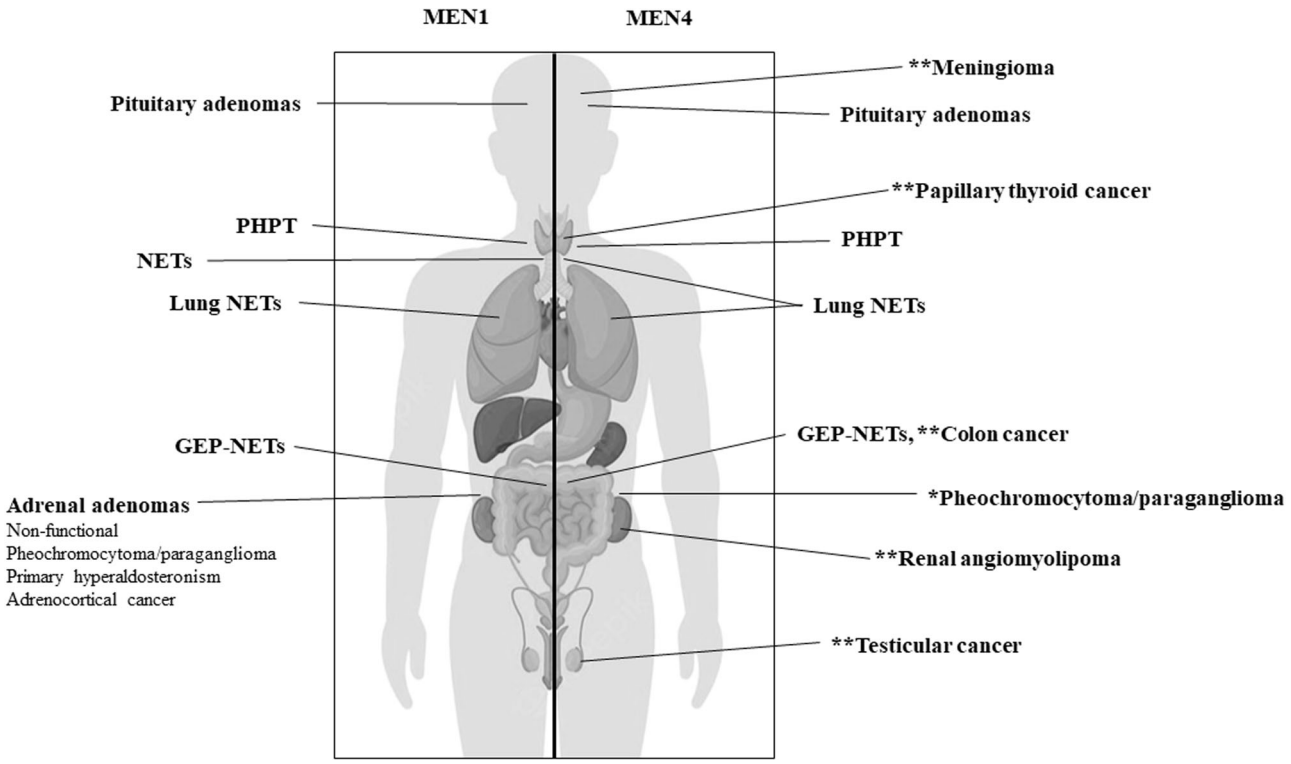

Fig. 2 Location of the most common benign and malignant tumors in MEN4 in comparison with MEN1 syndrome. *Only described in mouses with MEN4; **Paucity of data. GEP-NETs gastroenteropancreatic neuroendocrine tumors, NETs neuroendocrine tumors, PHPT primary hyperparathyroidism

RET, in accordance with the currently accepted guidelines [2, 59]. If negative, germline mutations in *CDKN1B* should be investigated with NGS in all patients with clinical features resembling the MEN1 syndrome but not carrying a *MEN1* pathogenetic variant [27].

Specific recommendations for MEN4 are lacking given the low number of cases reported in the literature. At the same manner, no guidelines currently exist regarding the genetic testing of asymptomatic relatives. All first-degree relatives of patients with MEN4 should be offered genetic testing since the MEN syndromes are transmitted in an autosomal dominant fashion. A negative genetic test result will offer reassurance to those who do not carry the mutation, and will prevent unnecessary clinical, biochemical, and radiological screenings. A positive genetic test result, on the other hand, should ensure inclusion into a surveillance program according to the risk profile of the respective MEN syndrome. In general, genetic testing and counseling for MEN should be performed by an experienced and specially qualified team.

The identification of a germline *CDKN1B* pathogenetic variants should prompt periodic clinical, biochemical and radiological screening that, due to the absence of specific guidelines, remains similar to that of MEN1 patients. In a recent review, Frederiksen et al. suggested to screen MEN4 patients for PHPT and PitAds in adolescence rather than in childhood, like for MEN1 patients, and to assess for NETs according to the guidelines provided for MEN1, considering the severe comorbidity associated with NETs and the lack of conclusive data on their real prevalence in MEN4 [58]. In MEN1, it is indeed recommended to investigate the presence of NETs even in asymptomatic subjects, performing periodic biochemical and imaging investigations [59].

Therapeutic options: surgery vs systemic therapies

At present, due the scarcity of reported cases and the lack of targeted clinical studies in the setting of MEN4, it is impossible to establish the optimal therapeutic algorithm and define the long-term outcomes in this cohort of patients: more data would be necessary. Regarding the most frequent clinical manifestations such as PHPT, PitAds and GEP-NETs current clinical practice may be complex and controversial, especially considering the multifocal and multiglandular nature of MEN4 and the up-to-date insufficient characterization of prognostic and predictive variables [27]. Available therapeutic strategies are summarized in Table 2.

Primary hyperparathyroidism

Currently, there are no standardized guidelines available for the management of MEN4 associated PHPT. Although

Table 2 Therapeutic options (surgery vs systemic therapies) for the main MEN4-related endocrine neoplasms

MEN4 manifestations		First-line treatment	Second-line treatment
PHPT		SPTX or TPTX with autologous reimplantation + transcervical thymectomy, LPX	Cinacalcet, Bisphosphonate
F-PitAd	ACTH-secreting (Cushing disease)	Surgery	Steroidogenesis enzyme inhibitors, Cortisol receptor blocker, SSAs, DA, RT
	GH-secreting (Acromegaly)	Surgery	SSAs, GH receptor antagonist, DA, RT
	PRL-secreting	DA	Surgery, RT, Temozolomide
NF-PitAd		Surgery/watchful surveillance	Insufficient data to suggest the routine use of medical therapy (i.e., DA, SSA)
GEP-NETs	Non-functioning	Surgery	SSAs, PRRT, CHT Future potential therapeutic options: TKI, mTOR inhibitors, E3 ubiquitin ligase SKP2 small-molecule inhibitors
	Gastrinoma (Zollinger-Ellison syndrome)	Surgery	PPI, SSAs

PHPT primary hyperparathyroidism, *PTH* parathyroid hormone, *SPTX* subtotal parathyroidectomy, *TPTX* total parathyroidectomy, *LPX* less-than-subtotal parathyroidectomy, *F-PitAd* functioning pituitary adenoma, *ACTH* adrenocorticotropic hormone, *SSAs* somatostatin analogs, *DA* dopamine agonizts, *RT* radiotherapy, *GH* growth hormone, *PRL* prolactin, *MRI* magnetic resonance imaging, *CT* computed tomography, *NF-PitAd*, clinically non-functioning pituitary adenoma, *GEP-NENs* gastroenteropancreatic neuroendocrine tumors, *PRRT* peptide receptor radionuclide therapy, *CHT* chemotherapy, *TKI* tyrosine kinase inhibitors, *mTOR* mammalian target of rapamycin, *SKP2* S-phase kinase-associated protein 2, *PPI* proton pump inhibitors

MEN4 appears to exhibit milder PHPT clinical and biochemical aberrations than MEN1, surgery represents the treatment of choice and the indications for surgical intervention may be analogous to those of MEN1 [27, 58]. As in MEN1, also in the context of MEN4-related PHPT whether parathyroidectomy is the optimal approach remains questionable, and an individualized algorithm regarding the extent of the parathyroid excision is necessary [50]. The potential surgical options include total parathyroidectomy with heterotopic autotransplantation of parathyroid tissue in the non-dominant forearm of the patient, or subtotal parathyroidectomy, which consists in the resection of three or three and a-half glands [60, 61]. In order to reduce the rate of a major post-operative complication such as permanent hypoparathyroidism, a feasible alternative may also include less-than-subtotal parathyroidectomy (LPX) [60]. The indolent nature of MEN4 associated PHPT, the frequent involvement of one single parathyroid gland and the rare incidence of persistence/recurrence of PHPT, support the need for individualized minimal surgery [58]. Thus, in specific cohorts of patients LPX or the excision of the single parathyroid adenoma may be considered [50]. Moreover, due to the paucity of reported case, to date there are no specific indications for the optimal timing of surgery. Whereas parathyroidectomy is associated with a reasonable risk/benefit ratio in symptomatic patients with severe hypercalcemia to treat and prevent the related complications, the programming of such an intervention in young patients with asymptomatic and mild hypercalcemia warrants further studies [1, 60]. The only curative treatment for PHPT is surgery, however, pharmacological management with calcimimetic agents (Cinacalcet) and antiresorptive therapy (bisphosphonates) should be evaluated in case of patients' refusal of parathyroidectomy or when surgery is not recommended due to significant comorbidities, contraindications, or prior unsuccessful neck exploration [62].

Pituitary adenomas

PitAds generally appear to be less aggressive in MEN4 than in MEN1 patients, however their clinical course is heterogeneous due to the functional status, size, potential invasive behavior and histological features [27]. To date, there are no specific guidelines regarding the management of MEN4 related PitAds. Thus, therapeutic strategies may follow the standardized recommendations for sporadic PitAds or for tumors in other familial settings and include surgery, medical therapy and radiotherapy accordingly [27, 58]. Generally, surgery, mainly performed by endonasal transsphenoidal approach and rarely by craniotomy, represents the first-line therapy in case of pituitary apoplexy, mass effects such as compression of the optic chiasm with eventual visual field defects, and all functioning adenomas except prolactinomas [63]. The two more frequent functioning PitAds reported in the context of MEN4 include somatotropinomas and corticotropinomas, which are

primarily surgically managed with a curative intent [6, 58]. After initial adenomectomy, pharmacological options with somatostatin analogs (SSAs), pegvisomant and cabergoline may be considered for acromegaly, meanwhile ketoconazole, mifepristone and pasireotide for Cushing's disease [63]. In contrast, prolactinomas, which to date represent the rarest functioning pituitary tumors in MEN4 patients, require first-line medical therapy with dopamine agonizts [6, 58]. Systemic treatment with the alkylating agent temozolomide may be considered for particularly aggressive prolactinomas and for pituitary carcinomas, although so far this approach gave scarce benefits [63]. Clinically non-functioning and asymptomatic microadenomas (<10 mm) require follow-up and may be addressed surgically in case of tumor enlargement or mass effects occurrence [1, 63]. Moreover, as for non-syndromic or MEN1 associated PitAds, also in MEN4 adjunctive radiotherapy may be reserved to selected cases that after initial surgical and/or medical therapies did not achieve sufficient tumor growth reduction nor biochemical control [1, 64].

Gastroenteropancreatic neuroendocrine neoplasms

At present, due to the lack of standardized recommendations for NETs in MEN4 patients, current clinical practice is similar to MEN1 [27, 59]. To date, a few cases of NETs in the setting of MEN4 have been reported comprising prevalently nonfunctional GEP-NETs and gastrinomas among the functional tumors [6, 27, 58]. Surgery is the only curative intervention for both functional and nonfunctional NETs and should be considered as first-line treatment in case of localized, nonmetastatic and small neoplasms [65]. Regarding nonfunctional pancreatic NETs (NF-pNETs), because of the paucity of data and no clear correlation between the risk of metastasis/post-operative recurrence and the tumor size, we suggest that, as in MEN1, surgical resection should be recommended for tumors larger than 2 cm, and should be evaluated for those larger than 1 cm as well as for NF-pNETs smaller than 1 cm but with significant growth rate, such as dimension doubling over 3- to 6-months reaching more than 1 cm in size [59]. The optimal treatment for gastrinomas causing Zollinger−Ellison syndrome remains controversial and should be established case-by-case. Localized and nonmetastatic pancreatic gastrinomas could be addressed surgically, whereas in case of multiple duodenal gastrinomas surgical intervention may not be feasible [59]. Thus, similar to MEN1 associated gastrin-secerning lesions, when tumor resection is not possible, pharmacological therapy including proton-pump inhibitors and SSA should be considered [27, 59]. In case of inoperable, locally advanced or metastatic NETs, medical therapy needs to be evaluated. Pharmacological options may include SSAs, i.e., lanreotide or octreotide, and peptide receptor radionuclide therapy (PRRT) if the tumors are well-differentiated and somatostatin receptor (SSTR)-positive, or chemotherapeutic regimens if they are poorly-differentiated neoplasms with aggressive behavior [66]. Since NETs express tyrosine kinase (TK) receptors, the potential efficacy of TK inhibitors (TKI), such as sunitinib, could be explored in MEN4 pNETs. This agent is a multikinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors, which are necessary for tumor growth and survival [60]. Another rationale for the potential evaluation of TKI in this subset of patients is supported by an accumulating knowledge regarding the signaling pathway of *CKDN1B*/p27. Specifically, p27 down-regulation caused by proteasome-dependent proteolysis is related to poor prognosis and disease progression in many human cancers [27, 67]. Reduction or loss of p27 expression is stimulated by the pro-oncogenic activation of several TK such as phosphatidylinositol 3-kinase (PI3K), proto-oncogene tyrosine-protein kinase Src, or MAPKs [27, 68, 69]. Therefore, the impact of targeting TK receptors may be studied both in patients affected by MEN4-associated NET as well as in carriers of somatic *CKDN1B* mutations [27]. Moreover, the proteasomal degradation of p27 is also mediated by the E3 ubiquitin ligase S-phase kinase associated protein 2 (SKP2), which is regulated by PI3K/protein kinase B (AKT) pathway [70]. There is evidence that PI3K signaling may activate mTOR complex 2 (mTORC2) and that mTORC2 may interfere with the modulation of the SKP2/p27 axis. Specifically, mTORC2 stimulates the reduction of nuclear p27 protein expression through the increased protein levels of SKP2 [71]. Therefore, mTOR inhibitors, such as everolimus, could play a role in limiting p27 down-regulation and their impact could be investigated as a potential future therapeutic approach also in MEN4 patients [71]. Last but not least, given the role of SKP2 in p27 degradation, small-molecule inhibitors of this ubiquitin ligase could represent a viable medical option to consider and explore for the treatment of GEP-NETs in the context of MEN4 [72].

Conclusions and future perspectives

As the number of MEN4 cases reported in the literature has increased over the years, both similarities and differences with respect to MEN1 have been emerging. MEN4 shares with MEN1 the development of a wide spectrum of endocrine and non-endocrine neoplasms, the most common clinical manifestations being PHTP, PitAds and GEP-NETs in both syndromes. However, MEN4 differs from MEN1 for a later onset and milder clinical features. Therefore, these patients might need specific diagnostic and therapeutic approaches and a different strategy for screening and

follow-up. Pathogenetic variants of *CDKN1B*, encoding for the cell-cycle regulator p27, have been identified in MEN4 patients. Further studies are needed to assess the real oncological risk of MEN4 carriers, and to establish a standardized screening protocol. Furthermore, a deeper understanding of p27 modulation and function in MEN4 is needed in order to explore p27 as a novel therapeutic target by developing specific intervention strategies in these patients.

Acknowledgements This study is part of the 'Neuroendocrine Tumors Innovation Knowledge and Education' project led by Prof. A.M.I, Prof. A.C and Prof. A.F which aims at increasing the knowledge on neuroendocrine tumors. We would like to acknowledge all the Collaborators of the "NIKE" project.

Author contributions Each Author gave a substantial contribute to the paper and approved the final version to be published.

Funding This work was not supported by any grant.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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