17 Neuroendocrine Neoplasms with Peculiar Biology and Features: MEN1, MEN2A, MEN2B, MEN4, VHL, NF1

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Abbreviations

AKT	Protein kinase B
ATA	American Thyroid Association
CDK	Cyclin-dependent kinase
CEA	Carcinoembryonic antigen
CLA	Cutaneous lichen amyloidosis
CT	Computed tomography
DOPA	3,4-Dihydroxyphenylalanine
d-pNET	Duodeno-pancreatic NET
EUS	Endoscopic ultrasound
FDG	Fluorodeoxyglucose
FNA	Fine-needle aspiration
GEP	Gastroenteropancreatic
GLP-1R	Glucagon-like peptide-1 receptor
gNET	Gastric NET
HIFs	Hypoxia-inducible factors
MEN1	Multiple endocrine neoplasia type 1
MEN2	Multiple endocrine neoplasia type 2
MEN4	Multiple endocrine neoplasia type 4
MIBG	Metaiodobenzylguanidine
MiNEN	Mixed neuroendocrine non-neuroendocrine neoplasm
MRI	Magnetic resonance imaging
MTC	Medullary thyroid cancer
mTOR	Mammalian target of rapamycin
NEC	Neuroendocrine carcinoma
NEN	Neuroendocrine neoplasm
NET	Neuroendocrine tumor
NF1	Neurofibromatosis type 1
PD1	Programmed cell death protein 1
PDGF	Platelet-derived growth factor polypeptide
PET	Positron emission tomography
PFS	Progression-free survival
PGL	Paraganglioma
PHEO	Pheochromocytoma
PHPT	Primary hyperparathyroidism
PI3K	Phosphoinositide 3-kinase
pNEN	Pancreatic NEN
PNMT	Phenylethanolamine N methyltransferase
PPIs	Proton pump inhibitors
PRRT	Peptide receptor radionuclide therapy
RET	Rearranged during Transfection
SPECT	Single photon emission computed tomography

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G. Beretta et al. (eds.), *Neuroendocrine Neoplasia Management*,
https://doi.org/10.1007/978-3-030-72830-4_17

SSAs	Somatostatin analogs
SST	Somatostatin
SUV	Standardized uptake value
TGFα	Transforming growth factor α
TKI	Tyrosine kinases inhibitor
US	Ultrasound
VEGF	Vascular endothelial growth factor
VHL	Von Hippel–Lindau disease
VIPoma	Vasoactive intestinal polypeptidoma
WDHA	Watery diarrhea, hypokalemia, and achlorhydria
ZES	Zollinger–Ellison syndrome

17.1 Introduction

A subgroup of neuroendocrine neoplasms (NENs) show a hereditary background and occur in the context of genetic endocrine neoplastic syndromes, such as multiple endocrine neoplasia type 1 (MEN1), multiple endocrine neoplasia type 2 (MEN2), variants MEN2A and MEN2B, multiple endocrine neoplasia type 4 (MEN4), Von Hippel–Lindau disease (VHL), and neurofibromatosis type 1 (NF1) [1–5]. It has been estimated a rate around 10% of patients with gastroenteropancreatic (GEP) NENs associated with a hereditary endocrine neoplastic syndrome [1, 2]; this rate is higher in case of pancreatic NENs (pNEN), while thyroid NENs are associated with MEN2 in 20–30% of cases [6].

The genetic origin of the neoplasm greatly influences its natural history, since the diagnosis of NEN is generally made toward the sixth decade of life in the case of sporadic forms, while the forms associated with hereditary syndromes are diagnosed approximately two to three decades in advance, sometimes in adolescence [1, 7]. NENs associated with hereditary syndromes are generally well differentiated, the so-called neuroendocrine tumors (NET), low proliferating, multiple, and multifocal [1, 2]. MEN1-related duodeno-pancreatic NETs (d-pNETs) are in most cases grade 1 or 2, while no case of neuroendocrine carcinoma (NEC) is generally found [2].

D-pNETs are found in 70–80% of patients with MEN1, while VHL is associated with pNET in up to 30% and NF1 with dNET in 1% of cases [8–12]. These tumors are frequently associated with functioning endocrine syndromes and highly express somatostatin (SST) receptors. MEN2A and B are mainly characterized by the development of thyroid NET, the so-called medullary thyroid cancer (MTC), in about 100% of cases [6]. Lung and thymic carcinoids as well as gastric NET (gNET) arise in less than 10% of MEN1 patients [8]. Together with malignant tumors, neuroendocrine adenomas could arise in these genetic syndromes. Pituitary and parathyroid adenomas are common in MEN1, while they represent the main lesions of MEN4 [8, 13]. Parathyroid adenomas also develop in MEN2A [8]. Pheochromocytoma (PHEO) is common in MEN2 (~50%), VHL (10–20%), and less common in NF1 (~5%) [14]. Extra-adrenal PHEO, the so-called paragangliomas (PGLs), can occur in VHL as well as NF1. These tumors frequently result in hormone hypersecretion syndromes, such as hyperprolactinemia, hyperparathyroidism, and hypersecretion of catecholamines. Rarely adrenomedullary tumors and very rarely pituitary as well as parathyroid tumors present malignant behavior in patients with hereditary endocrine neoplastic syndromes. Other tumors of non-neuroendocrine origin are described in all the hereditary syndromes associated with NEN. They are less frequent in MEN1, MEN2, and MEN4, while VHL and NF1 represent the main manifestations and have negative prognostic impact [1–5].

An update of diagnosis and treatment of NENs in patients with MEN1, MEN2A, MEN2B, MEN4, VHL, NF1 is here described.

17.2 MEN1

17.2.1 Overview

MEN1 is an autosomal dominant genetic syndrome characterized by the occurrence of NENs arising mainly in parathyroid glands, pancreatic islet cells, and anterior pituitary gland [8]. The syndrome is caused by mutations in the tumor suppressor *MEN1* gene, located on chromosome

11 (11q13), consisting of 10 exons, encoding a 610 amino acid nuclear protein, named menin [15]. Menin, in association with 50 different proteins, contributes to DNA repair, cell signaling, cytoskeletal structure, cell division, adhesion, and motility. The main mechanism underlying tumorigenesis related to menin loss in MEN1 syndrome needs to be fully elucidated [16]. Phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling pathway, which appears to be inhibited by menin [17, 18], is shown in Fig. 17.1.

In 90% of patients, the mutation is inherited from an affected parent, and only in 10% there is a de novo *MEN1* germline mutation [19]. Currently, contrary to what occurs in MEN2, a clear correlation between phenotype and genotype has not been found [20].

The prevalence of MEN1 is 1–10/100,000 [21]. It has been estimated to be 1–18% in patients with primary hyperparathyroidism

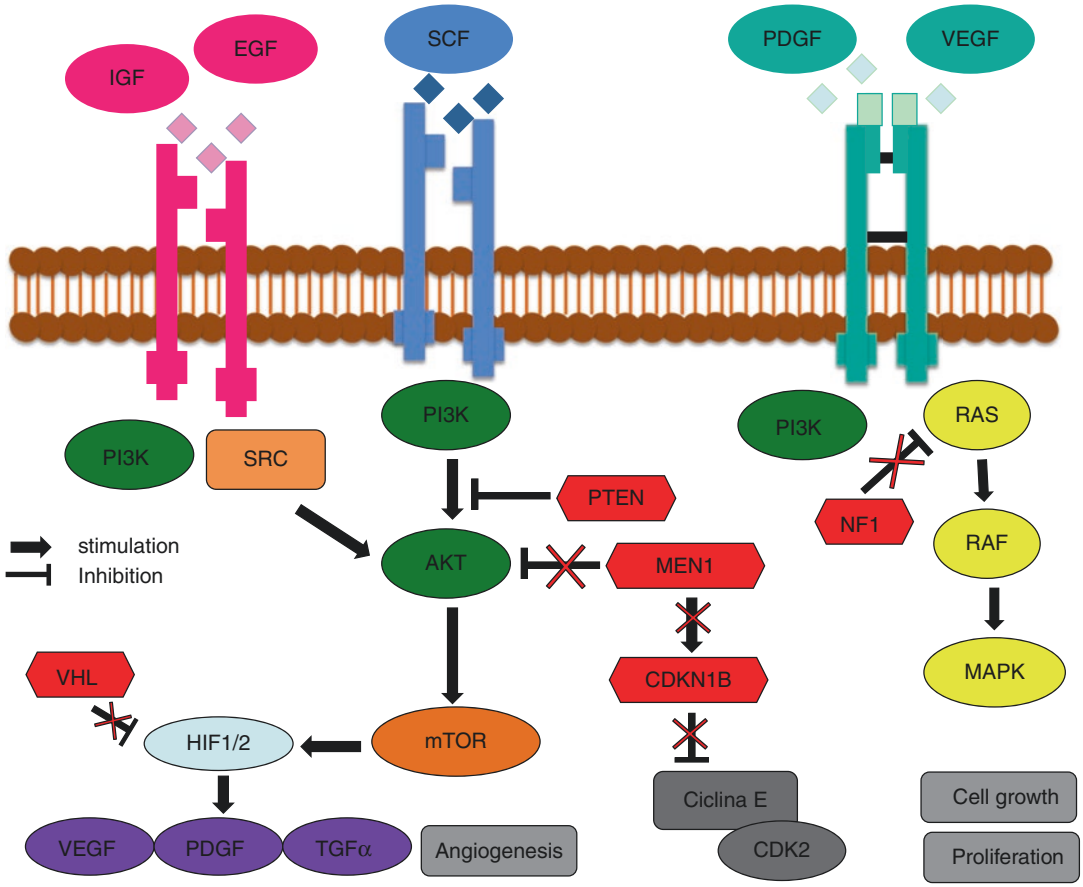

Fig. 17.1 Molecular pathogenesis of NENs in hereditary endocrine neoplastic syndromes (MEN1, MEN4, VHL, NF1). The red boxes indicate onco-soppressor genes acting by negative regulation of various pathways involved in cell growth and proliferation (PI3K/AKT/mTOR; RAS/RAF/MAPK; p27/Ciclina E/CDK2) and angiogenesis (HIF1/2). The inactivating mutations of these genes are responsible of oncogenic events in the corresponding syndrome (MEN1, MEN4, VHL and NF1). *IGF* insulin growth factor, *EGF* epidermal growth factor, *SCF* stem cell factor, *PDGF* platelet derived growth factor, *VEGF* vascular endothelial growth factor, *PI3K* phosphoinositide 3-kinase, *SRC* sarcome tyrosine kinase, *AKT* protein kinase B, *mTOR* mammalian target of rapamycin, *PTEN* phosphatase and tensin homolog, *VHL* Von Hipple Lindau, *HIF* hypoxia inducible factor, *TGFα* transforming growth factor, *MAPK* mitogen activated protein kinase, *MEN1* multiple endocrine neoplasia type 1, *CDKN1B* cyclin-dependent kinase inhibitor 1 B, *CDK2* cyclin-dependent kinase 2, *NF1* neurofibromatosis type 1

(PHPT), 16–38% in patients with gastrinomas, and <3% in patients with pituitary adenomas [8]. The syndrome affects patients with an age ranging from 5 to 81 years [8].

The syndrome can be diagnosed using the 2012 Endocrine Society Clinical Practice Guidelines criteria as follows: (1) clinical diagnosis, occurrence of at least two endocrine tumors typically associated with MEN1, (2) familial diagnosis, presence of one MEN1-related tumor in a first-degree relative of a patient with a clinical diagnosis of MEN1, (3) genetic diagnosis, detection of a germline *MEN1* mutation in an asymptomatic subject with no evidence of tumor by biochemical or imaging examination [8].

The typical MEN1 manifestations are PHPT, occurring in >90% of patients and due to adenoma/hyperplasia generally involving all parathyroid glands, pituitary adenomas, occurring in 30–40% of cases and characterized by prolactin hypersecretion in about half of cases, and NENs, which are observed in 70–80% of patients, mainly located within pancreas and duodenum but also found in other sites within digestive and respiratory system [8, 10] (Table 17.1).

17.2.2 MEN1-Related NEN: Diagnostic and Therapeutic Update

Among NENs, those arising in duodenum and pancreas are the most frequent in MEN1 (up to 80% of cases) [8, 10]. MEN1-related NENs are divided into functioning and non-functioning tumors. A variety of hormones are secreted excessively by functioning tumors such as gastrinomas, insulinomas, glucagonomas, vasoactive intestinal polypeptidomas (VIPomas), and several of them are associated with specific clinical syndromes [8] (Table 17.2).

Non-functioning tumors could be either non-secreting or secrete inactive polypeptides such as pancreatic polypeptide, chromogranin A, neurotensin, neuron-specific enolase, or ghrelin. In most cases, such tumors are detected incidentally or, rarely, patients could exhibit symptoms related to tumor mass. In case of functioning tumors, the clinical features are dependent on the secreted hormone. Gastrinoma's clinical presentation often includes abdominal pain, heartburn, nausea, gastrointestinal bleeding, and diarrhea (steatorrhea) [22, 23]. The presence of hypergastrinemia and recurrent peptic ulcerations, caused by the secretion of gastrin, allow the diagnosis of Zollinger–Ellison syndrome (ZES) which occurs in 21–70% of patients with MEN1 [8, 21, 24]. Insulinomas cause fasting hyperinsulinemic hypoglycemia accompanied by autonomic and neuroglycopenic symptoms [22, 23]. The pathognomonic combination of necrolytic migratory erythema, weight loss, anemia, and stomatitis may be absent in MEN1-related glucagonomas, so they can be detected just by glucose intolerance and hyperglucagonemia [8, 22]. Watery diarrhea, hypokalemia, and achlorhydria (WDHA) are characteristics of the Verner–Morrison syndrome (WDHA syndrome), caused by VIPomas [8].

Contrary to the sporadic counterpart, MEN1-related d-pNENs occur at a younger age and are multifocal and generally well-differentiated, low-grade tumors (G1-G2 NET) [2, 25, 26]. Moreover, the presence of d-pNENs in patients with MEN1 is correlated with an increased mortality [10, 27, 28], and tumor size has been proven to be directly related to a higher risk of metastatization and death regardless of hormone secretion [29, 30]. Another factor which is independently associated with an increased risk of distant metastases is the presence of ZES [29, 31]. Nevertheless, ZES, which used to be the major cause of death in patients with MEN1 [21], nowadays, seems not associated with an increased mortality; however, this evidence needs further confirmations [27–29].

Bronchopulmonary and thymic NENs occur in about 2% of MEN1 patients, gNENs (the type II gastric carcinoid of the clinical classification) in <10%, and PHEOs in <1% [8] (Tables 17.2 and 17.3). Thymic NENs in MEN1 are particularly aggressive and are associated with a significantly increased risk of death, even in absence of distant metastases [29].

Table 17.1 Phenotypic spectrum across the hereditary endocrine neoplastic syndromes

	PHPT	Pituitary adenoma				MTC	PTC	ACA	PHEO	PGL	Gastroenteropancreatic NET					Lung carcinoid	Thymic carcinoid	NEC
											Duodenum–Pancreas				Stomach			
		PRL	GH	ACTH	NF						ZES	INS	Other	NF				
MEN1	X	X	X	X	X		X	X	X		X	X	X[a]	X	X	X	X	
MEN2A	X					X			X	X								
MEN2B						X			X									
MEN4	X	X	X	X	X		X	X			X			X	X	X		X[b]
VHL	X								X	X				X				
NF1									X	X		X	X[c]	X				

PHPT primary hyperparathyroidism, *PRL* prolactin, *GH* growth hormone, *ACTH* adrenocorticotrophic hormone, *NF* non-functioning, *MTC* medullary thyroid cancer, *PTC* papillary thyroid cancer, *ACA* adrenal cortex adenoma, *PHEO* pheochromocytoma, *PGL* paraganglioma, *NET* neuroendocrine tumor, *ZES* Zollinger–Ellison syndrome, *INS* insulinoma, *NEC* neuroendocrine carcinoma

[a]Glucagonoma, vipoma

[b]Small cell cervical NEC reported in one case

[c]Somatostatinoma

Table 17.2 Main features of neuroendocrine neoplasms associated with hereditary endocrine neoplastic syndromes: comparison with the sporadic counterpart

Neuroendocrine neoplasms					
	MEN1	MEN4	VHL	NF1	Sporadic tumors[a]
Rate of NENs	Up to 80%	17%	20%	1%	–
Age at tumor diagnosis	<50 years	50–60 years	35 years (mean age)	<50 years	56–66 years (mean age)[b]
M:F ratio	1:1.4	Only F	1:1.1 to 1:1.6	M=F	M>F (si-, d-, p-, rNET) F>M (g-, a-, ceNET)
Site (from high to low frequency)	Pancreas, duodenum, stomach, lung, thymus	Pancreas, duodenum, stomach, lung, cervix	Pancreas	Duodenum and peri-ampullary region, pancreas, rectum	All sites
Histology	Well differentiated low tumor grade (G1–G2 NET) No G3 reported	Well differentiated low tumor grade (G1 NET/ typical carcinoid) NEC in cervix	Well differentiated low tumor grade (G1–G2 NET) G3 NET extremely rare	Well differentiated low tumor grade (G1–G2 NET) Psammoma bodies in SSoma	Well differentiated (G1–G3 NET): 90% Poorly differentiated (NEC): 10%
Metastases at diagnosis	13.7%	Metastases in 4/8 cases (lymph node and distant)	Rare distant metastasis at diagnosis	Common lymph nodes, rare distant metastases	G1 NET: 21% G2 NET: 30% G3 NET or NEC: 50%
Clinical manifestation (from high to low frequency)	– Non-functioning: incidental diagnosis, symptoms in case of complications – ZES – Insulinoma – Extremely rare: VIPoma; glucagonoma; SSoma	– Non-functioning: incidental diagnosis, local symptoms – ZES	– Non-functioning: incidental diagnosis, symptoms in case of complications	– Non-functioning: incidental diagnosis, local symptoms, pain, and jaundice – SSoma (often asymptomatic) – Insulinoma	– Non-functioning: incidental diagnosis, symptoms in case of complications – Carcinoid syndrome – ZES – Insulinoma – Rare: VIPoma; glucagonoma, SSoma
Neuroendocrine markers	CgA, specific markers according to clinics	CgA, gastrin	CgA NSE	CgA, specific markers according to clinics	CgA, NSE, specific markers according to clinics
Conventional imaging	Gastrointestinal endoscopy, endoscopic US, CT/MRI	Gastrointestinal endoscopy, endoscopic US, CT/MRI	Endoscopic US, CT/ MRI	Gastrointestinal endoscopy, endoscopic US, CT/MRI	Gastrointestinal endoscopy, endoscopic US, CT/MRI
Functional imaging	^{68}Ga-DOTA PET-CT (^{18}F-FDG PET-CT)	^{68}Ga-DOTA PET-CT (^{18}F-FDG PET-CT)	^{68}Ga-DOTA PET-CT (^{18}F-FDG PET-CT)	^{68}Ga-DOTA PET-CT (^{18}F-FDG PET-CT)	^{68}Ga-DOTA PET-CT (^{18}F-FDG PET-CT)

Treatment	– Radical surgery in d-pNET ≥2 cm or tumor growth rate >0.5 cm/year or functioning tumor (if possible, enucleation) – Radical surgery in lung/thymic NEN – Endoscopic resection in gNET >1 and <2 cm – Surveillance in non-functioning nonprogressive d-pNET <2 cm and gNET <1 cm (SSA alternative approach) – SSA in unresectable/ metastatic disease and, in case of progression, PRRT or targeted therapy – CHT in metastatic tumors non-responsive to previous therapies	– Radical surgery in d-pNET ≥2 cm or tumor growth rate >0.5 cm/year or functioning tumor (if possible, enucleation) – Radical surgery in lung NEN – Endoscopic resection in gNET >1 and <2 cm – Surveillance in non-functioning nonprogressive d-pNET <2 cm and gNET <1 cm – SSA in unresectable/ metastatic disease and, in case of progression, PRRT or targeted therapy – CHT in metastatic tumors non-responsive to previous therapies or NEC	– Radical surgery in pNET >2 cm (if possible, enucleation) – Surveillance in pNET <2 cm – SSA in unresectable/ metastatic disease and, in case of progression, PRRT or targeted therapy – CHT in metastatic tumors non-responsive to previous therapies or rare G3 NET	– Radical surgery (pancreaticoduodenectomy) in d-pNET >2 cm (local resection if possible) – Endoscopic resection or transduodenal surgical ampullectomy in small tumor (<1–2 cm) – SSA in unresectable/ metastatic disease and, in case of progression, PRRT or targeted therapy – CHT in metastatic tumors non-responsive to previous therapies or MiNEN	– Radical surgery in local and locoregional NET if resectable – Enucleation or endoscopic resection, if possible, in stage I tumors, according to tumor site, size, grade, and presence of functioning syndrome – Surveillance in non-functioning nonprogressive pNET <2 cm and d-gNET <1 cm – SSA in unresectable/ metastatic disease and, in case of progression, PRRT or targeted therapy – CHT in metastatic tumors non-responsive to previous therapies or G3 NEN

yrs years, *M* male, *F* female, *NEN* neuroendocrine neoplasm, *NET* neuroendocrine tumor, *siNET* small intestine NET, *dNET* duodenal NET, pancreatic NET, *rNET* rectal NET, *gNET* gastric NET, *aNET* appendiceal NET, *ceNET* cecum NET, *NEC* neuroendocrine carcinoma, *VIP* vasoactive intestinal polypeptide, *ZES* Zollinger–Ellison syndrome, *SS* somatostatin, *CgA* chromogranin A, *NSE* neuron-specific enolase, *US* ultrasound, *CT* computed tomography, *MRI* magnetic resonance imaging, *PET* positron emission tomography, *FDG* fluorodeoxyglucose, *MIBG* metaiodobenzylguanidine, *SSA* somatostatin analog, *PRRT* peptide receptor-targeted radiotherapy, *CHT* chemotherapy, *MiNEN* mixed neuroendocrine non-neuroendocrine neoplasms

[a]References: Garcia-Carbonero et al. ENETS Consensus Guidelines for High-Grade Gastroenteropancreatic Neuroendocrine Tumors and Neuroendocrine Carcinomas, Neuroendocrinology. 2016;103(2):186–94; Cives M, Strosberg JR. Gastroenteropancreatic Neuroendocrine Tumors.CA Cancer J Clin. 2018 Nov;68(6):471–87

[b]Mean age at diagnosis was younger in appendiceal NEN

Table 17.3 Main features of pheochromocytoma and paraganglioma associated with hereditary endocrine neoplastic syndromes: comparison with the sporadic counterpart

Pheochromocytoma and paraganglioma						
	MEN1	MEN2A	MEN2B	VHL	NF1	Sporadic tumors[a]
Rate of PHEO/PGL	<1%	70–80% of MEN2	5% of MEN2	10–20%	7.7–14.6%	–
Age at tumor diagnosis	<50 years	<35 years	<35 years	<30 years	>40 years	30–50 years
M:F ratio	M = F	M = F	M = F		F>M (++ malignant tumors)	M=F
Site (from high to low frequency)	Monolateral PHEO, rarely bilateral Anecdotical PGL	Multicentric and bilateral PHEO 65% of cases Metachronous in up to 25% of cases	Multicentric and bilateral PHEO 65% of cases Metachronous in up to 25% of cases	Mostly PHEO, usually multiple and bilateral Less frequent PGL (more functioning)	85% monolateral adrenal PHEO 9.6% bilateral PHEO, 6% PGL	Mostly monolateral PHEO
Malignancy rate	15%	1–4%	1–4%	5%	11.5%	10–17%
Clinical manifestation (from high to low frequency)	Symptomatic: hypertension, headache, sweating, palpitations, flushing	– Symptomatic: hypertension, headaches, sweating – Asymptomatic in 1/3 at the time of diagnosis	– Symptomatic: hypertension, headaches, sweating – Asymptomatic in 1/3 at the time of diagnosis	– Symptomatic: mostly related to norepinephrine secretion – Rarely dopamine secretion or asymptomatic	– Asymptomatic: incidental diagnosis – Symptomatic related to epinephrine and norepinephrine secretion	– Symptomatic: hypertension, headache, sweating, palpitations, flushing – Asymptomatic: incidental diagnosis or mass effect
Neuroendocrine markers	Plasma free or urinary fractionated metanephrines	Plasma free or urinary fractionated metanephrines	Plasma free or urinary fractionated metanephrines	Plasma free or urinary fractionated metanephrines, (methoxytyramine)	Plasma free or urinary fractionated metanephrines, (methoxytyramine)	Plasma free or urinary fractionated metanephrines
Conventional imaging	CT or MRI	CT or MRI	CT or MRI	CT or MRI	CT or MRI	CT or MRI for adrenal mass; MRI for extra-adrenal mass
Functional imaging	^{123}I-MIBG (^{18}F-DOPA PET-CT/ ^{18} FDG PET-CT)	^{123}I-MIBG (^{18}F-DOPA PET-CT/ ^{18} FDG PET-CT)	^{123}I-MIBG (^{18}F-DOPA PET-CT/ ^{18} FDG PET-CT)	^{123}I-MIBG (^{18}F-DOPA PET-CT/ ^{18} FDG PET-CT)	^{123}I-MIBG ^{18}F-DOPA PET-CT	^{123}I-MIBG In metastatic disease: ^{18} FDG PET-CT

Treatment	– Laparoscopic adrenalectomy for primary tumors – ^{131}I-MIBG-PRRT, CHT, sunitinib, everolimus for metastatic tumors	Laparoscopic cortical sparing adrenalectomy Total adrenalectomy for recurrence	Laparoscopic cortical sparing adrenalectomy Total adrenalectomy for recurrence	– Laparoscopic cortical sparing adrenalectomy for primary tumors – ^{131}I-MIBG/PRRT, CHT, sunitinib, everolimus for metastatic tumors	Laparoscopic adrenalectomy for small and unilateral tumors – Posterior retroperitoneoscopic adrenalectomy for large or bilateral tumors – Laparoscopic cortical sparing adrenal surgery for bilateral tumors – ^{131}I-MIBG, CHT, sunitinib for metastatic tumors	– Laparoscopic adrenalectomy for primary tumors – ^{131}I-MIBG/PRRT, CHT, sunitinib, everolimus for metastatic tumors

yrs years, *M* male, *F* female, *PHEO* pheochromocytoma, *PGL* paraganglioma, *CT* computed tomography, *MRI* magnetic resonance imaging, *MIBG* metaiodobenzylguanidine, *PET* positron emission tomography, *DOPA* dihydroxyphenylalanine, *FDG* fluorodeoxyglucose, *PRRT* peptide receptor-targeted radiotherapy, *CHT* chemotherapy

[a]Reference: Lenders JWM et al. Pheochromocytoma and Paraganglioma: An Endocrine Society Clinical Practice Guideline- J Clin Endocrinol Metab. 2014 Jun;99(6):1915–42. doi: 10.1210/jc.2014-1498

The importance of an early diagnosis is highlighted by the high prevalence and unfavorable prognostic significance of d-pNENs in MEN1.

As reported in the current guidelines, besides a clinical diagnosis associated with plasma biochemical evaluation of hyperexcreted hormones, there is not a well-established consensus for the best radiological screening of MEN1-related NENs [8]. The minimum suggested imaging protocol includes annual abdominal magnetic resonance imaging (MRI), contrast-enhanced triphasic computed tomography (CT), or endoscopic ultrasound (EUS) [8]. Chest CT or MRI performed every 1–2 years is recommended for the detection of thymic and bronchopulmonary NENs. In patients with hypergastrinemia, a gastroscopy with eventual biopsy every 3 years is performed to detect peptic ulcer and type II gastric carcinoids [8].

^{68}Gallium positron emission tomography (PET) is widely used in sporadic NEN diagnosis, staging, and restaging [32]. Moreover, it can also provide prognostic information [33] and lead to therapeutic decisions, e.g., cold or radiolabeled somatostatin analogs (SSAs) [34]. The high sensibility and specificity of ^{68}Gallium PET-CT has been demonstrated in detecting also MEN1-related NENs [35–37]. Its diagnostic accuracy is high in both primary and metastatic tumors [38]. Given its higher diagnostic performance, ^{68}Gallium PET-CT should replace ^{111}In-pentetreotide single-photon emission computed tomography (SPECT) in the diagnostic work-up of MEN1-related NENs [39] and should be included in the radiologic screening and follow-up of these patients due to its capability to significantly adjust patient's therapeutic management [35, 36]. ^{68}Gallium PET-CT should be considered in the diagnostic work-up also when an insulinoma is suspected. Contrary to preliminary studies using ^{68}Ga-DOTANOC PET-CT which showed a low detection rate of insulinomas, with a sensitivity of 25% [40], ^{68}Ga-DOTATATE/DOTATOC PET-CT can identify up to 90% of sporadic insulinomas, and in case of MEN1 syndrome could be able to exclude the presence of additional pancreatic lesions not detected by anatomic imaging [41, 42].

Recently, due to the overexpression of glucagon-like peptide-1 receptor (GLP-1R) in benign insulinomas [43], PET-CT with ^{68}Ga-NOTA–exendin-4 has been studied in these patients. This new functional imaging has shown to be highly sensitive in the localization of sporadic benign insulinomas [44] and seems promising also in MEN1-related insulinomas, with a potential role in leading selective and pancreas-sparing surgery [45].

^{18}F-Fluorodeoxyglucose (FDG) PET avidity in sporadic metastatic NENs is strongly related to tumor differentiation and WHO tumor grade [46]. Moreover, it has also a prognostic role, and, regardless of Ki-67 index and histologic classification, the overall survival of patients with a positive ^{18}F-FDG PET scan is significantly lower than negative ones [47]. Given its prognostic role, ^{18}F-FDG PET-CT is suggested in MEN1 patients to identify lesions with a higher malignant potential, above all for pancreatic [48], pulmonary, and thymic lesions [49].

Recently, EUS has emerged as the most sensitive technique to detect small and intrapancreatic tumors [50]. Among its advantages, EUS allows a precise evaluation of pNEN size and can be utilized to assess serial changes in pNEN dimensions. Finally, fine-needle aspiration (FNA) can be associated with EUS to obtain a histological diagnosis guiding the clinician in therapeutic decisions [9, 51].

Medical therapy to control gastric hypersecretion includes proton pump inhibitors (PPIs) and H_2 receptor antagonists [8]. Surgical management of gastrinomas is controversial; however, surgical excision is the suggested treatment for ZES-related gastrinomas >2 cm. Surgical technique should be tailored to the patients considering preoperative findings, patient history, and preference [8, 52]. A more extensive surgery, such as pancreaticoduodenectomy with lymphadenectomy, is not performed routinely because of its higher operative mortality and long-term complications [8, 52].

In MEN1 patients with insulinomas, surgery ranges from tumor enucleation to distal pancreatectomy or partial pancreatectomy. It is the gold standard treatment in case of non-metastatic disease [8, 52]. EUS-guided ethanol ablation and CT-guided radiofrequency ablation can be performed in selected cases [52]. Before surgery, and in case of recurrent and metastatic insulinoma, patients need medical treatment. Besides frequent carbohydrate meals, also diazoxide, SSAs, the mTOR inhibitor everolimus, peptide receptor radionuclide therapy (PRRT), or hepatic artery embolization is effective in controlling hypoglycemia [52].

Regarding the other rarer functioning NETs, a curative resection is recommended in patients with pNENs >2 cm, and SSAs is the treatment of choice to control the hormone-excess prior to surgery or for unresectable lesions [8, 52].

Surgical resection is indicated for non-functioning pNEN more than 1–2 cm in size or a doubling of tumor size, over a 3- to 6-month interval and exceed 1 cm in size. Enucleation or local resection is preferred over pancreaticoduodenectomy [8]. Conservative management is safe for patients with lesions of ≤2 cm and is associated with a low risk of disease-specific mortality [53, 54]. However, recent evidence suggested that treatment with lanreotide autogel can improve progression-free survival in MEN1-related pNENs <2 cm, so avoiding or delaying surgery in a significant rate of patients [55].

Surgical treatment with curative intent is the treatment of choice for resectable thymic and bronchial NENs and PHEOs [8].

Small type II gastric carcinoids (<1 cm) may be endoscopically surveilled. Endoscopic resection or local resection with partial or total gastrectomy is reserved for larger tumors.

Similarly to sporadic NENs, in case of non-resectable or metastatic disease, SSAs (octreotide or lanreotide) are considered the first-line treatment, while PRRT is now available for NENs progressing under SSAs. Targeted therapy (everolimus or sunitinib) and chemotherapy (streptozotocin, 5-fluorouracil, doxorubicine, capecitabine/temozolomide) are effective therapies that could be employed for progressive disease [8, 56].

17.3 MEN2

17.3.1 Overview

MEN2 is an autosomal dominant genetic syndrome characterized by the occurrence of NENs arising most commonly in thyroid and adrenal glands [57] (Table 17.1). MEN2 is further classified into two subcategories: MEN2A that also presents primary PHPT (20%–30%) and MEN2B. MEN2A is further categorized into the following four subtypes: (1) classical MEN2, (2) MEN2A with cutaneous lichen amyloidosis (CLA), (3) MEN2A with Hirschsprung disease (HD), (4) familial medullary thyroid cancer.

In both MEN2A and MEN2B, there is an occurrence of multicentric NEN formation in all organs where *REarranged during Transfection (RET)* proto-oncogene is expressed.

The syndrome is caused by mutations in the *RET* proto-oncogene, localized on chromosome 10q11.2, which encodes a receptor tyrosine kinase. It appears to transduce growth and differentiate signals in several tissues, particularly those arising from neural crest cells. Some cytogenetic mutations have been reported; these may involve intracellular and extracellular domains of the RET protein signaling pathway. The germline *RET* mutations in MEN2 result in a gain of function of this tyrosine kinase receptor. This is different from many other inherited predispositions to neoplasia that are due to heritable "loss-of-function" mutations that inactivate tumor suppressor proteins [57] (Fig. 17.2).

The majority of the mutations in MEN2A variants occur in the cysteine-rich region of RET protein's extracellular domain (coded by the genes in exon 10 and 11). Mutations in the intracellular tyrosine kinase 2 domain cause MEN2B-associated tumors. A single 918 Met to Thr mutation (M918T) in exon 16 is responsible for

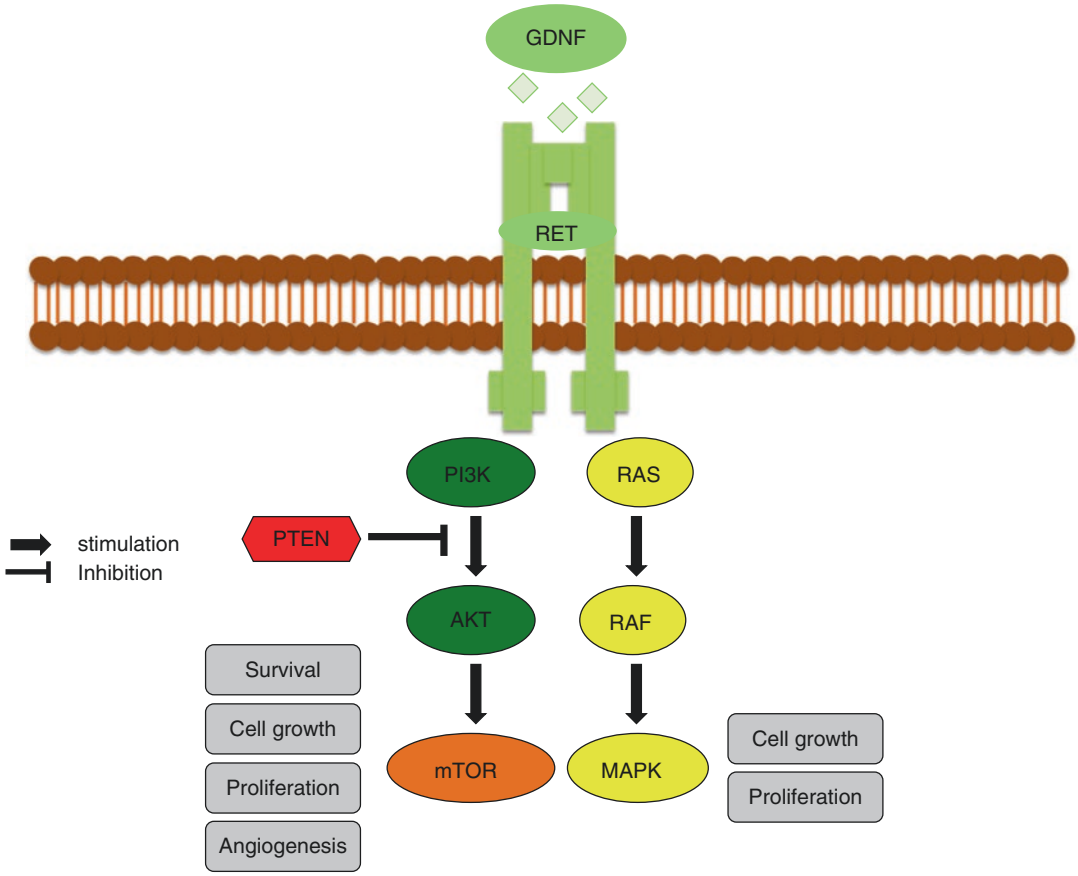

Fig. 17.2 Molecular pathogenesis of NENs in MEN2 syndrome. The proto-oncogene RET encodes for a Receptor Tyrosin Kinases that, activated by the GDNF-family ligands, regulates intracellular pathway involved in cell survival, growth, proliferation and angiogenesis. Constitutively activating mutations of RET are responsible of oncogenic event in MEN2 syndrome. *GDNF* glial cell-line-derived neutrophic factor, *RET* RErranged during Transfection receptor protein, *PI3K* phosphoinositide 3-kinase, *AKT* protein kinase B, *mTOR* mammalian target of rapamycin, *PTEN* phosphatase and tensin homolog, *MAPK* mitogen activated protein kinase

over 95% of cases of MEN2B. Other less common mutations are associated with both MEN2A and MEN2B divided into high-risk, moderate-risk, and low-risk categories [57–59].

The total prevalence of all MEN2 worldwide variants is approximately 1/35000. MEN2A accounts for about 95% of cases, MEN2B for 5%. In approximately 50% of MEN2B cases, a de novo germline *RET* mutation gives rise to the disease.

MEN2 should be suspected in any patient diagnosed with MTC or PHEO, particularly when the age of presentation is very young (<35 years). Any patient with diagnosed MTC or family history of MTC should be tested for *RET* proto-oncogene mutations for both MEN2A and MEN2B. The patients who are diagnosed with PHEO at an earlier age than sporadic forms should be tested for MEN2. The classic symptoms of PHEO are the paroxysms of a headache, anxiety, diaphoresis, palpitations, and high blood pressure. The presence of these symptoms in the third decade, particularly in between 25 and 32 years, should prompt to screen for MEN2 [57].

Other possible physical examination findings include marfanoid habitus (decreased upper to lower body ratio), mucosal neuromas (red papules) over lips and tongues, and joint hyperlaxity associated with MEN2B. MEN2A is also

suspected in patients with clinical features like purity, scaly, pigmented papules in the interscapular region, typical features of CLA [60]. The presence of PHPT alone does not indicate for further testing as it is less than 20% associated with MEN2A and no associated with MEN2B.

17.3.2 MEN2-Related NEN: Diagnostic and Therapeutic Update

17.3.2.1 MTC

Virtually all patients with MEN2A develop MTC. MTC is multicentric and occupies preferentially the upper and middle portions of each thyroid lobe. The tumor remains confined to the thyroid gland for a variable period of time before spreading to the regional lymph nodes and subsequently to the liver, lung, bone, and brain. Histologically, 20% of the tumors have a predominantly cellular growth pattern, 40% have a fibrous pattern with more than half of the cellular component replaced by a calcified acellular stroma, and the remaining 40% display an intermediate pattern with neoplastic nests of cells separated by bands of fibrous tissue. The stroma is composed primarily of full-length calcitonin, which has staining properties similar to amyloid [61].

The tumors should be appropriately staged using the synoptic cancer worksheets proposed by the College of American Pathologists [62]. Multifocality or C-cell hyperplasia in the contralateral lobe should be assessed, because those features indicate a strong likelihood of germline *RET* mutation and inherited disease [63].

It is important that clinicians who first see children with MEN2B recognize the characteristic signs and symptoms associated with the syndrome, because the MTC is highly aggressive in this setting, and there is a narrow window during which thyroidectomy may be curative [64–67].

Measurement of serum calcitonin levels, especially after the administration of the provocative secretagogues calcium, served as the primary method for screening family members at risk for hereditary MTC [68].

In line with the American Thyroid Association (ATA) management guideline for adult patients with thyroid nodules [63], the thyroid ultrasound (US) examination represents the first diagnostic choice. The US features suggestive of MTC could be hypoechoic, solid with smooth borders, round or oval shape nodule, and particularly the presence of micro- or macrocalcifications [69, 70].

The cytologic appearance of MTC on FNA can be variable, causing misdiagnosis with follicular neoplasm or sarcoma. A more accurate method of diagnosing MTC is to measure calcitonin in FNA washout fluid. FNA calcitonin is more sensitive than cytology for diagnosing MTC, reaching a 100% accuracy using a threshold value of 39.6 pg/mL (range reported in literature 7.4–67 pg/mL) [71], or a FNA calcitonin/serum calcitonin ratio >1.39 [72].

Immunocytochemistry staining of FNA specimens for calcitonin, carcinoembryonic antigen (CEA), and chromogranin can also be performed, increasing the sensitivity of cytology to 89.2% (95% CI: 74.6%–96.9%) [71].

The revised ATA guideline for MTC now recommends measurement of calcitonin in FNA washout fluid and immunocytochemistry for calcitonin, CEA, and chromogranin when cytology is inconclusive or suggestive of MTC (grade B recommendation based on fair evidence); however, the guideline does not recommend a threshold value for calcitonin [73]. CEA is not a specific MTC biomarker, but it is useful for monitoring disease progression. In addition, baseline levels of calcitonin can indicate distant metastases when they are higher than 500 pg/mL, recommending systemic imaging [74].

Approximately 50% of patients with MTC have metastatic disease on initial presentation [75]. Palpable thyroid nodules are associated with a 70% rate of lymph node metastasis and a 10% rate of distant metastasis [76].

Recommended imaging studies include neck US, CT of lungs and mediastinum, three-phase contrast-enhanced multi-detector liver CT or contrast-enhanced MRI of liver, and bone MRI or scintigraphy [77]. ^{18}F-FDG PET-CT and ^{18}F-dihydroxyphenylalanine [DOPA] PET-CT are less sensitive in detecting metastases and therefore are not recommended [78, 79].

Specific *RET* mutations are associated with disease aggressiveness and dictate early timing of thyroidectomy [80]. Before MTC is treated, diagnosis of a PHEO is essential to avoid a hypertensive crisis during surgery [80]. The preferred therapeutic option is total thyroidectomy with dissection of lymph nodes in the central neck. Additional lymph node compartments are dissected if there is evidence of metastases on preoperative imaging studies, or at the time of thyroidectomy. Currently, the generally accepted practice is to use a combination of genetic testing and the basal or stimulated serum calcitonin level to decide the timing of thyroidectomy. In families with hereditary MEN2B, the disease may be apparent at or soon after birth, when thyroidectomy may be curative; however, the MTC is aggressive in this setting, and rarely, infants have regional lymph node metastases at the time of thyroidectomy [81].

Lifelong follow-up is indicated, beginning every 3 months postoperatively, and at longer intervals if there is no evidence of persistent or recurrent disease in the first year after thyroidectomy. Serial measurements of serum calcitonin and CEA levels are useful in documenting disease progression, and especially their the doubling time.

For the patients with persistent or recurrent MTC, the treatment option is systemic therapy with orally available tyrosine kinases inhibitors (TKI), such as vandetanib, a selective inhibitor of RET, vascular endothelial growth factor receptor (VEGFR), and epidermal growth factor receptor (EGFR) signaling, and cabozantinib, targeting MET, VEGFR2 and RET [82]. Recently LIBRETTO 001 (NCT03157128), a phase I-II trial on the efficacy of selpercatinib, a selective RET inhibitor, has been published. In RET-mutated thyroid cancer, including also a group of 55 patients affected by MTC, objective response was 69% [83]. Phase III trial comparing selpercatinib with cabozantinib or vandetanib in tirosin kinase naive patients is currently ongoing (NCT 04211337). Another selective *RET* inhibitors (BLU-667, Blueprint Medicines, Inc., Cambridge, MA, USA) is currently being evaluated in a phase II clinical trial (NCT03037385).

17.3.2.2 Pheochromocytomas and Paragangliomas

PHEOs develop in approximately 50% of patients with MEN2A and MEN2B, the clinical presentation and behavior are similar in the two syndromes. The mean age of presentation is 36 years, and the diagnosis is made after MTC in 50% of cases, concurrently with MTC in 40% of cases, and before MTC in 10% of cases. In patients with PHEO, the adrenal tumors are almost always benign and confined to the gland. In 65% of cases, they are multicentric and bilateral. Patients with unilateral PHEO usually develop a contralateral PHEO within 10 years [84].

There is significant morbidity and mortality associated with an undiagnosed PHEO; thus, in patients with known MEN2A or MEN2B, it is critical to rule out this tumor before interventional procedures. In MEN2B, over 90% of patients with PHEO have gastrointestinal symptoms characterized by abdominal pain, constipation, and alternatively diarrhea, bloating, and megacolon. The gastrointestinal symptoms are particularly evident in children and young adults and may require a surgical procedure to relieve symptoms [85]. Of note, about one-third of the patients were not symptomatic (hypertension, headaches, sweating) at the time of diagnosis [86]. Then systematic screening should thus be performed regularly even in the absence of clinical signs suggestive of PHEO.

The development of PHEO in MEN2 is usually progressive, and bilateral PHEOs are not always synchronous: metachronous PHEOs have been reported in up to 25% of cases after a mean period of 5–10 years [86, 87], requiring a prolonged follow-up after the first surgery. PHEO represents the most prevalent disease of MEN2 given the fact that young familial cases are treated by prophylactic thyroidectomy.

Positive diagnosis is based on increased plasma metanephrines and normetanephrines (drawn from a supine patient after an overnight fast), or 24-h urinary fractionated metanephrines and normetanephrines or plasma or urinary fractionated metanephrine and normetanephrine [88]. MEN2-associated PHEOs express phenylethanolamine N methyltransferase (PNMT), the

enzyme that converts norepinephrine to epinephrine, hence the association with predominant epinephrine secretion and elevated metanephrines [88]. Serum chromogranin A is elevated in 48% of patients with PHEO [88]. Diagnostic utility of chromogranin A is, however, constrained by poor specificity due to its elevation in several conditions [88].

Imaging should be performed only when biochemistry becomes positive [89]. US can detect PHEO in 80–90% of cases [90] where it may be visible as a well-defined mass, which may be solid (75% in one case series) or cystic or mixed [91]. CT scanning and MRI are used to localize PHEO. The sensitivity (90%–100%) and specificity (70%–80%) are similar for the two procedures [92, 93].

Several specific radiopharmaceuticals (^{123}I-metaiodobenzylguanidine [MIBG], ^{18}F-DOPA PET, and ^{111}In-pentetreotide (Octreoscan, Covidien) and ^{68}Gallium PET) have been used for functional imaging [92, 94, 95]. The main advantage of ^{18}F-DOPA compared to other radiopharmaceuticals is the absence or faintly uptake by normal adrenal glands. ^{18}F-DOPA PET-CT can also detect residual MTC in patients with persistent hypercalcitoninemia [96–100]. MIBG is the most common and available functional imaging used in the assessment of PHEO. The uptake of radiotracer is proportional to the number of neurosecretory granules within the tumor [92, 94, 95]; therefore, the characteristic appearance of a PHEO is unilateral focal uptake within the tumor [101]. Octreoscan and ^{68}Gallium PET can detect PHEO, because they express SST receptors [95].

Excepting very unusual circumstances, a PHEO should be resected before the MTC if both are present. Preoperative preparation is with alpha-adrenergic blockade and if necessary beta-adrenergic blockade. Subtotal sparing adrenalectomy is indicated to preserve adrenocortical function [102, 103]. The idea of adrenal sparing surgery is to take off the PHEO while maintaining one third to one fourth of the gland to allow maintenance of a normal cortisol and aldosterone function. As there is only a very low 1–4% risk of malignancy for MEN2 PHEO [104], this procedure should be systematically considered in all patients with MEN2 PHEO. The standard procedure is laparoscopic adrenalectomy [105, 106]. Recurrence after adrenal sparing surgery will be mainly treated by total adrenalectomy, or in some very experienced centers, by another partial adrenalectomy [107].

17.4 MEN4

17.4.1 Overview

MEN4 is a recently characterized autosomal dominant genetic syndrome characterized by the occurrence of NETs arising mainly in parathyroid glands and anterior pituitary gland [13]. The syndrome is caused by mutations in the tumor suppressor *CDKN1B* gene, located on chromosome 12 (12p13), consisting of three exons, encoding a kinase inhibitor protein named p27, primarily inhibiting the complex cyclin E/cyclin-dependent kinase (CDK)2 [108] (Fig. 17.1). MEN4 is generally observed in patients with MEN1 phenotype but no *MEN1* gene mutations, the so-called MEN1 phenocopies, or patients with an intermediate phenotype between MEN1 and MEN2 without *MEN1* and *RET* mutations. The incidence of *CDKN1B* mutations in MEN1 phenocopies has been estimated in the range of 1.5–3.7% [109, 110]. To date, 48 subjects have been reported as *CDKN1B* mutated, including 23 MEN4 patients and 25 carriers. Nineteen different heterozygous loss-of-function *CDNK1B* mutations have been identified in patients with MEN4, including nine missense, six nonsense or frameshift, and four mutation/deletion within the 5'-UTR region [109–123]. As a whole, *CDKN1B* mutations causing MEN4 affect p27 cellular localization, stability, or biding with Cdk2 or Grb2 [108].

All typical MEN1 endocrine tumors are observed also in MEN4 (Table 17.1). As in MEN1, PHPT is the most frequent endocrine disorder in MEN4 (83%), while pituitary adenoma occurs in 39% and is mostly ACTH- and GH-secreting, conversely to MEN1 where the prolactin-secreting adenoma is the main type.

NENs presented a lower penetrance in MEN4 than MEN1, being reported in 17% of the *CDKN1B* positive subjects reported in the literature. However, the rate of NENs is double (35%) if we consider the 23 cases with MEN4 reported.

17.4.2 MEN4-Related NEN: Diagnostic and Therapeutic Update

Due to the very small number of cases, it is not possible to achieve specific conclusions for MEN4-related NENs. These included GEP NEN in six cases, lung and cervix in one case each [109, 110, 112, 114, 116, 117, 120, 123] (Table 17.2). All GEP NENs were well-differentiated tumors (NET) as well as the lung one, which was a typical carcinoid. A small cell poorly differentiated cervical NEC occurred in one patient. Among the GEP NETs, four were pNET, in combination with dNETs in three cases, and two gNET. A ZES was the only functioning endocrine syndrome, reported in two patients with d-pNETs. No other functioning syndrome such as insulinoma, glucagonoma, VIPoma, and ectopic hormone syndrome has been reported. When reported, Ki-67 index was 1% (G1). Three pNET, two of whom associated with dNETs, were metastatic, as well as the lung carcinoid, while the gNETs were localized.

In all cases, NENs were diagnosed in females at age ranging 42–79 years (median, 57 years). In all cases but one, a PHPT was also detected, while pituitary adenomas were in three out of the eight patients with NEN (acromegaly, Cushing's disease, and nonfunctioning pituitary adenoma respectively).

As a whole, a diagnosis of MEN4 has to be considered in all patients with MEN1-related tumors and no *MEN1* mutation. MEN4-related NENs are usually NETs located within the duodenum–pancreas tract. They are well differentiated and low proliferating, resulting in tumor diagnosis in the sixth decade as average.

In the lack of specific studies for MEN4-related NENs, the diagnostic work-up of these tumors should be made in the same way as for MEN1 NENs, where contrast-enhanced triphasic CT scan or MRI, in combination with EUS, is the best diagnostic procedure to detect the small NETs which are located in duodenum and pancreas. Endoscopy and EUS are the optimal tool to characterize gNETs. As for either MEN1 or sporadic NETs, ^{68}Gallium PET is the best functioning imaging technique in MEN4-related NETs, to perform tumor staging in combination with CT, as well as to candidate these tumors to therapy with cold or radiolabeled SSAs.

As for MEN1, ZES can be associated with MEN4 d-pNETs and should be therefore investigated by measuring serum gastrin levels, after exclusion of all other conditions of hypergastrinemia, first of all the use of PPIs. Chromogranin A is the general neuroendocrine marker to be assessed after the histological diagnosis of NET, as potentially useful biochemical marker for follow-up.

An optimal strategy to perform an early diagnosis of NEN in MEN4, is to perform the mutational analysis of *CDKN1B* in all patients with MEN1 phenotype and negative *MEN1* analysis. Care should be in particular for females affected with PHPT.

When a MEN4 patient is identified, a familiar genetic screening has to be performed in order to recognize asymptomatic patients and gene carriers. All *CDKN1B*-positive subjects should undergo a clinical, biochemical, and radiological work-up, which has to be addressed not only to parathyroid glands and pituitary but also to NENs, in particular d-pNETs.

Therapy of MEN4-related GEP NENs could be the same as in MEN1. Surgery has to be considered for tumors >1.5–2.0 cm within pancreas or duodenum or tumor progressing during active surveillance or those associated with ZES. As in MEN1, radical surgery has not to be taken in account because of high morbidity and mortality rate, while tumor enucleation, distal pancreatectomy, and duodenectomy are reasonable procedures for this kind of patients.

SSAs are the first therapeutic option in MEN4-related d-pNETs with uncontrolled ZES or tumor progression. MEN4-related GEP NENs are expected to be clinically controlled and

radiologically stabilized for long time with SSA therapy. In case of SSA failure, PRRT is a new option for all SST-positive tumors. MEN4 NETs likely express SST at high grade and therefore are potential candidates for PRRT. Alternatively, a targeted-therapy with everolimus could be performed, especially in consideration of the peculiar molecular pathway underling these tumors, where the AKT-mTOR complex results to be hyperactivated. Finally, chemotherapy is another option that could be considered in metastatic NETs with high tumor burden, not responding to previous therapies.

17.5 Von Hippel–Lindau

17.5.1 Overview

VHL disease is an autosomal dominant genetic syndrome caused by a germline mutation in the *VHL* gene. *VHL* is a suppressor gene located on chromosome 3p25 [124]. This gene has three exons which encode for two different mRNA and, consequently, two isoforms of VHL protein [125]. Both the isoforms are required for VHL protein actions. *VHL* is a tumor suppressor gene, so tumors arise in patients after the inactivation of the wild-type allele. VHL protein, localized in the nucleus or cytoplasm, binds elongin B, elongin C, and Cullin 2 [126]. The multi-protein complex is responsible of the inhibition of transcription elongation and ubiquitin-mediated degradation of various proteins, including the α subunits of hypoxia-inducible factors (HIFs) 1 and 2 [127] (Fig. 17.1). Consequently, abnormal or absent VHL protein is implicated in tumorigenesis by enhancing HIFs and, consequently, stimulating glucose uptake and expression of angiogenic and mitogenic factors as VEGF, platelet-derived growth factor (PDGF), and transforming growth factor α (TGFα) [4, 128, 129].

Prevalence of VHL disease is 1/36,000 live births [4]; the majority of VHL cases are familial but up to 20% are caused by de novo mutations [130]. Penetrance is almost complete by the age of 75 years [131]. VHL patients show inherited susceptibility to many kinds of benign and malignant tumors including renal clear cell carcinoma, hemangioblastomas of the retina and of the central nervous system, endolymphatic sac tumors, simple cysts, pancreatic serous cystadenomas, and NENs [132]. Clinically, VHL syndrome is classified into two types according to the absence (type 1) or presence (type 2) of PHEO. Type 1 can be subclassified in accordance with high (1A) or low (1B) risk of renal cell carcinoma. Type 2 VHL is further categorized into type 2A (associated with other tumors different from renal cell carcinoma), type 2B (associated with renal cell carcinoma), and type 2C (only PHEO, also called autosomal dominant familial non-syndromic PHEO). Interestingly, different family members can have different disease manifestations as well as different VHL subtypes [133, 134].

Clinical diagnosis is based on the discovery of a classical VHL-associated tumor (central nervous system hemangioblastoma, retinal hemangioblastoma, renal cell carcinoma, PHEO) in a patient with positive familial history or, for sporadic cases, diagnosis is based on the presence of at least two classical VHL-associated tumors (in particular, two hemangioblastomas or one hemangioblastoma associated with one visceral tumor) [133]. Genetic testing is always recommended for confirmatory diagnosis, familial screening, genetic counseling, and genotype-phenotype predictions [132, 135]. The identification of asymptomatic carriers of *VHL* mutation is essential for early detection of VHL-related tumors in order to limit morbidity and mortality [135, 136].

NENs associated with VHL include pNENs and PHEO/PGLs, while PHPT is anecdotally reported (Table 17.1).

17.5.2 VHL-Related NEN: Diagnostic and Therapeutic Update

17.5.2.1 Pancreatic NEN

Patients with VHL syndrome have a lifetime risk of developing one or more pNENs of 20%. Table 17.2 reports the main features of VHL-associated pNETs. Histologically, VHL-related

pNETs are similar to the sporadic counterpart, even if they can present clear cell features [137]. Classical neuroendocrine cells are medium size, uniform cells with eosinophilic cytoplasm, round to oval nuclei, and "salt-and-pepper" granular chromatin, usually organized in trabecular structures [138]. Similarly to MEN1-, MEN4-, and NF1-related NENs, VHL-related NENs are usually grade 1 or 2 NETs. Women have a slightly higher risk of pNET development, with male to female ratio ranging from 1:1.1 to 1:1.6 [139, 140]. Mean age of presentation is 35 years, about 20 years before sporadic pNET [141]. The youngest patient affected by pNET was 11 years old [141]. Half of these tumors are localized in the head of the pancreas [142]. VHL-related pNETs differ from sporadic ones because of their tendency to be multiple [143] but with overall indolent behavior, even if a variable proportion of patients ranging, in larger studies or metanalysis, from 12.8 to 20% have metastatic disease [141, 144].

The great part of VHL-associated pNETs are non-functioning [139], and only sporadic reports demonstrated that they can secrete ACTH, causing ectopic Cushing's syndrome [145]. Patients are therefore usually asymptomatic, and symptoms arise in case of compression of nearby structures [146].

Diagnosis is based on radiological findings. Morphological imaging commonly used for the detection of pancreatic lesions are contrast-enhanced CT and MRI and EUS [147]. CT shows a well-defined solid mass, usually with rounded or lobulated borders, characterized by early enhancement [148]. Pancreatic MRI usually shows hypointense T1-weighted sequences and hyperintense T2-weighted sequences lesions, which can contain hemorrhagic, necrotic, and calcified portions [149]. EUS is the most sensitive method for the diagnosis of small solid pancreatic tumors [147]. Functional imaging is recommended in case of locally advanced or metastatic disease; moreover, it could play a role for helping differential diagnosis and for identifying tumor recurrence [147]. In sporadic pancreatic tumors, ^{68}Gallium-DOTA PET showed a better sensibility compared to SST receptor scintigraphy [39, 150]. This data has been confirmed also in VHL-associated pNET [141, 151]. In a study on 197 patients affected by VHL-related pancreatic lesions, Sadowski et al. demonstrated that ^{18}F-FDG PET-CT was able to correctly characterize pNETs using a standardized uptake value (SUV) cut-off of 4 (sensibility 92%, specificity 75%) and in three patients also gave the possibility to recognize metastatic sites not previously detected by total-body CT scan [152]. Routine use of biopsy in these patients is not recommended, because tumors are nearly often correctly identified by morphological and functional imaging, and pNET in VHL disease are known to be well differentiated, although a biopsy would be useful to characterize tumor biology in selected patients [147]. Chromogranin A can be useful for follow-up in some patients with high basal levels [153].

Natural history of pNET is variable among VHL patients, so it is of a great importance to consider prognostic factors in order to identify the best treatment strategy.

Blansfield et al., in a study on 108 VHL-related pNETs, described that more aggressive tumors, with higher metastatic potential, had three characteristics: size >3.0 cm, presence of a mutation in exon three and tumor doubling time less than 550 days [139]. Similarly, Krauss et al. underwent to comparable conclusions: size >2.8 cm and mutation in codon 161/167 of exon three were the main prognostic factors [141].

According to these findings, surgical resection is the therapy of choice for larger masses. Guidelines recommended surgery in case of diameter >3.0 cm in pancreatic tail and body, considering the higher risk of metastases, and >2.0 cm in pancreatic head and uncinate process, in order to prevent main pancreatic duct involvement, which implicates a more radical resection [147]. After guidelines publication, an original article on 2330 VHL patients, 273 of which had pNETs, demonstrated a longer 10 years disease-free survival also in small pNET surgically treated compared to surveillance [154]. On the other hand, surgically treated patients had a high rate of postoperative complications. In particular, early postoperative complications were fistula,

abscess, or cholangitis (23%), while long-term postoperative complications were diabetes mellitus and exocrine insufficiency (41%) [141]. Taking into account ENETS consensus guidelines for the management of pNET [52], it is reasonable to suggest a surgical resection of VHL pNETs with one of the following characteristics: diameter >2.0 cm, growth rate >0.5 cm per year or in case of functioning tumors.

In case of surgical resection, given the possibility of multiple lesions, intraoperative US should be suggested [155]. When it is possible, enucleation of pNETs is recommended for sparing pancreatic tissue [143], even if no comparison study between enucleation and classical resection is currently available. Lymphadenectomy is recommended for correct staging [147].

After surgical excision, annual imaging with CT or MRI is recommended [155]. In case of locally advanced or metastatic disease, no specific data are available in VHL patients, so patients are treated according to the beforementioned ENETS guidelines [52]. Briefly, surgical intervention can be considered for reducing tumor burden or in case of complications, as obstruction, compression, or hemorrhage [147]. Systemic first-line therapy is based on SSAs, which has demonstrated in CLARINET study to increase progression-free survival (PFS) in entero-pancreatic NETs [156]. In case of disease progression, it is possible to consider PRRT [52] or targeted therapy [157]. Specific targeted therapies could play an important role in VHL-related tumors, even if no dedicated clinical trials are currently available in VHL-mutated patients.

17.5.2.2 Pheochromocytomas and Paragangliomas

PHEO/PGLs arise respectively from chromaffin cells localized in the adrenal medulla and in extra-adrenal paraganglia. The percentage of VHL patients developing PHEO/PGLs is estimated from 10 to 20% [4, 132]. Table 17.3 reports the main features of VHL-associated PHEO/PGLs. For definition, PHEO occurs only in type 2 VHL. Mean age of presentation is <30 years, and the risk of malignancy is lower than 5% [158]. More than 900 *VHL* mutations have been described, including deletions, missense substitutions, and mutations causing the synthesis of a truncated protein. PHEO often occurs in association with specific alleles, usually due to missense mutations rather than deletions or premature termination [125]; particularly, the mutation at nucleotide 238 in exon 3 is associated with a 62% risk for PHEO [159]. The reason could be that PHEO development requires partial but not complete loss of function in VHL protein [134]. Interestingly, HIF-2α is highly expressed in the adrenal medulla and in the organ of Zuckerkandl, and the gene encoding for tyrosine hydroxylase, implicated in adrenal catecholamine production, is a HIF target gene [160].

PHEO in VHL disease can be bilateral and multiple [4] and most commonly secrete norepinephrine, although a small percentage can produce dopamine [161]. Clinical presentation includes intermittent or sustained hypertension, palpitations, tachycardia, headaches, anxiety, sweating, pallor, and flashes up to hypertensive crisis [130].

PHEO/PGLs are histologically characterized by neoplastic cells, with oval nuclei, granular cytoplasm, and evident nucleolus, gathered in nest or "zellballen" pattern, surrounded by S-100-positive sustentacular cells [132, 138].

Diagnosis is based on the dosage of plasmatic or urinary fractionated metanephrines. Plasmatic normetanephrines seem to have the greatest sensitivity and specificity compared to other plasma catecholamines and urinary catecholamines, and vanillylmandelic acid [162]. Urinary fractionated metanephrines can be used alternatively [163]. Endocrine Society Clinical Practice guidelines on PHEO/PGL recommend drawing blood sample for plasma testing in supine position, using liquid chromatography with mass spectrometric or electrochemical detection methods and checking possible pharmacological interferences [163].

Confirmatory clonidine suppression test demonstrated 97% sensibility and 100% specificity in a retrospective study [164], but no data are available in VHL syndrome, and this test should be performed in centers with an adequate experience and only in selected patients.

In case of biochemical alterations, morphological imaging is recommended. CT is usually preferred for the detection of adrenal masses, considering the great sensibility and special resolution, while MRI is more accurate for PGL identification [163]. PHEOs/PGLs appear as homogeneous or heterogeneous mass, usually necrotic, with some calcifications [165]. MRI usually shows hyperintense mass in T2-weighted image [166].

Functional imaging is particularly relevant in case of extra-adrenal PGLs or for metastatic disease. Guidelines recommend ^{123}I- MIBG scintigraphy for the high accuracy in PHEO diagnosis (sensibility 92%, specificity 94%) [167] and for predicting response to radiotherapy using ^{131}I-MIBG. In metastatic cases, diagnostic accuracy of ^{18}F-FDG PET seems better than ^{123}I-MIBG [168]. Few studies analyzed diagnostic accuracy of ^{18}F-DOPA PET-CT in VHL-related PHEOs/PGLs. Weisbrod et al., in a study on 52 VHL-mutated patients, demonstrated that ^{18}F-DOPA PET-CT was able to identify lesions not detected by conventional imaging in 9.6% of patients, even if CT and MRI generally identified a larger amount of masses. The authors concluded that ^{18}F-DOPA PET-CT should be used as complementary diagnostic technique [169]. Another study on 101 patients, including 19 VHL mutated patients, with known or suspected PHEOs/PGLs, demonstrated a high sensibility and specificity of ^{18}F-DOPA PET-CT, respectively 93% and 88% [170].

Surgery is the treatment of choice and should be performed even in asymptomatic patients. Best surgical management for VHL-associated PHEO is laparoscopic cortical sparing mass excision, in order to maintain corticosteroid independence [171, 172]. In case of functioning PHEO/PGL, patients require previous preparation therapy with α-adrenergic receptor blockers. Objectives of pre-surgical treatment are reduction of diastolic blood pressure and heart rate, and minimization of the risk of postoperative hypotension [173].

β-Adrenergic receptor blockers are indicated for controlling tachycardia but can be used only after starting α-adrenergic receptor blockers, and calcium antagonist can be added for controlling blood hypertension [174].

In metastatic PHEOs/PGLs, debulking surgery can improve overall survival [175]. In case of stable disease or slow progression, a follow-up strategy or radionuclide therapy using ^{131}I-MIBG or ^{177}Lu-DOTATATE is recommended [176].

Systemic treatment includes chemotherapy with cyclophosphamide, vincristine, and dacarbazine. This protocol is burdened by serious adverse events and determines a partial response in about 37% of patients [177].

Recently, new targeted therapies are under evaluation for the treatment of metastatic PHEOs/PGLs. Antiangiogenic therapy with TKI has been studied as potential treatment in malignant lesions [178], and an international randomized study on sunitinib is now ongoing (FIRSTMAPPP, NCT01371201). Sunitinib seems particularly promising in VHL syndrome, considering the role of sustained angiogenesis in VHL mutated tumors [179].

Finally, immunotherapy has been proposed in patients with alterations in proteins associated with the regulation of hypoxia-inducible factor-α, as in VHL disease [176, 180]. The programmed cell death protein 1 (PD1) is one of the checkpoints that impedes the efficacy of cytotoxic T lymphocyte response, and pembrolizumab is a humanized monoclonal antibody directed against PD1 [181]. Only one phase II trial on pembrolizumab is now recruiting (NCT02721732), and the results could be very interesting for VHL-associated PHEO/PGL.

VHL guidelines [131, 182, 183] recommend that screening for PHEO/PGL should begin in early childhood (5 years) and should be repeated every 12 months, using blood pressure monitoring and evaluation of fractionated metanephrines (paying special attention to normetanephrine) in plasma or 24-h urine collection. Imaging protocol includes annually abdominal US examination from 8 to 15 years, reserving MRI or functional imaging in case of biochemical alterations. After the age of 16 years, abdominal imaging is performed annually, alternating abdominal US and

MRI, which is preferred to CT for reducing exposure to ionizing radiation. Clearly, abdomen examination is performed also for the early diagnosis of renal cell cancer and pNET.

17.6 Neurofibromatosis Type 1

17.6.1 Overview

NF1, also known as von Recklinghausen disease, is an autosomal dominant disorder with a complete penetrance and variable expression, caused by germline mutations in the *NF1* tumor suppressor gene. *NF1* gene, located on chromosome 17q11.2, encodes for neurofibromin, a protein acting as negative regulator of the RAS-RAF-MAPK pathway, involved in cell growth and proliferation (Fig. 17.1). So the loss of neurofibromin expression, as seen in NF1, leads to increased cell growth and survival through hyper-activation of RAS. NF1 belongs to a group of inherited disorders referred to as phakomatoses or neurocutaneous syndromes.

Its prevalence is estimated in 1/3000 live births, with half of cases showing a family history and half arising with a de novo mutation. NF1 can affect multiple organ systems and has a wide range of variable clinical manifestations.

Approximately all individuals with NF1 develop pigmentary lesions (café-au-lait macules, skinfold freckling, and Lisch nodules) and dermal neurofibromas. Some individuals show skeletal abnormalities (scoliosis, tibial pseudarthrosis, and orbital dysplasia), brain tumors (optic pathway gliomas and glioblastoma), peripheral nerve tumors (spinal neurofibromas, plexiform neurofibromas, and malignant peripheral nerve sheath tumors), learning disabilities, attention deficits, and social and behavioral problems, which can negatively affect the quality of life. Life expectancy in people with NF1 is reduced by 10–15 years mainly due to a high risk of malignant tumors [184]. NENs can occur in the context of NF1 including either GEP NENs or PHEOs/PGLs (Table 17.1).

17.6.2 NF1-Related NEN: Diagnostic and Therapeutic Update

17.6.2.1 Gastroenteropancreatic NEN

NF1-related GEP NENs (Table 17.2) are reported in about 1% of individuals with NF1 with special affinity for the duodenal and periampullary region [185]. In the most recent review of gastrointestinal tumors associated with NF1, tumor sites were duodenum (60%), ampulla (31%), pancreas (5%), or bile duct/gallbladder (4%), with SST-positive NET, the so-called somatostatinoma, as the most common histology (40%) [5]. The peri-ampullary somatostatinoma is almost patognomonic of NF1, because a rate of 26–41% of these tumors has been reported in association with NF-1 [5]. A recent study of whole-exome sequencing of six NF1-related dNETs confirmed the importance of somatic inactivation of the wild-type *NF1* and suggested that loss of chromosome 22 is another genetic determinant in at least a subset of cases [186].

The NF1 somatostatinomas, compared to sporadic ones, occur at younger age (<50 years) and are smaller in size, probably because of the earlier diagnosis due to local symptoms (i.e., pain and jaundice) related to peri-ampullary localization and the clinical screening of this kind of NET in the context of NF1 [185]. They are well differentiated (NET), with low tumor grade (G1–G2) and high incidence of psammoma bodies (psammomatous calcifications), which are helpful in guiding the diagnosis. Very rarely mixed neuroendocrine non-neuroendocrine neoplasms (MiNENs) of periampullary region, expressing SST, have been reported [187]. The majority of peri-ampullary and dNENs in NF1, although express SST, are non-functioning somatostatinomas, so they occur in the absence of the characteristic syndrome, including diabetes mellitus, steatorrhea, cholelithiasis, and weight loss. Most patients with gastrointestinal tumors associated with NF1 are symptomatic (92%), but clinical features are variable depending on tumor localization, size, and spread [5].

The most frequent symptoms are attributed to the mass effect: jaundice and non-specific abdominal pain are the most common, occurring in approximately two thirds of patients, followed by weight loss, gastrointestinal bleeding, and anemia. Due to the high risk of NF1-related malignancies, patients with abdominal symptoms may show one or more intra-abdominal, synchronous, or metachronous tumors, especially gastrointestinal stromal tumors, associated with dNETs [188].

The imaging features of a peri-ampullary mass in a patient with NF1 are clinically relevant in making the differential diagnosis, since somatostatinoma usually presents as a focal intraluminal mass [185].

Since these tumors express SST receptor subtypes 2 and 5, SST receptor-based imaging techniques are useful to localize them, but also to predict the response to therapy with cold or radiolabeled SSAs. Therefore, the ^{68}Gallium-DOTATATE PET-CT, in combination with upper gastrointestinal endoscopy, EUS, CT, and MRI should be considered for diagnosis, staging, and preoperative assessment of these tumors [189].

In NF1 individuals, NETs very rarely metastasize. Local and node invasions are more frequent, but the preoperative imaging study and endoscopic biopsy are often inaccurate regarding lymph node involvement and depth of invasion [190].

For tumors smaller than 1–2 cm, there is no consensus regarding management. Endoscopic excision or transduodenal surgical ampullectomy have been suggested [191]. Endoscopic ampullectomy could be an option when the tumor is limited to the mucosal layer without lymphovascular involvement [190]. Otherwise, transduodenal surgical ampullectomy could be suggested for relatively small tumors with suspected submucosal invasion [190]. However, ENETS guidelines for gastroduodenal sporadic NETs smaller than 1 cm suggest a more aggressive approach for peri-ampullary lesions with surgical resection, whereas an endoscopic management for not peri-ampullary localizations. On the contrary, for NF1-related NETs ≥2 cm, surgical resection is recommended, and local lymphadenectomy should also be considered due to the risk of submucosal invasion and lymph node involvement. Pancreaticoduodenectomy with regional lymphadenectomy should be limited to larger tumors with more aggressive behavior. Postoperative treatments in cases with node metastases have not been established. Response to chemotherapy with etoposide and cisplatin has been reported in a metastatic NET [190], while to 5-fluoroacil and oxaliplatin in a patient with MiNEN [192].

pNETs in NF1 patients are rare with only seven cases reported in the literature, five of them showed an aggressive behavior, suggesting that might be some biological differences between peri-ampullary and pancreatic NF1-related NETs. Histology was insulinoma in three cases, somatostatinoma in two cases, and non-functioning NET in two other cases [193].

In only two NF1 patients, rectal NETs have been described. They were multiple, with different and nonspecific clinical symptoms, that include changes in bowel habits, hematochezia, and abdominal pain. This clinical picture is similar to those of the most frequent rectal diseases such as hemorrhoids, rectal polyps, and colorectal adenocarcinoma, thus making difficult to achieve an early diagnosis [194].

17.6.2.2 Pheochromocytomas and Paragangliomas

PHEOs/PGLs in patients with NF1 (Table 17.3) show a debatable prevalence. While the mostly cited prevalence in the literature is 0.1–5.7% based on a retrospective review [195], subsequent studies showed that the prevalence might be higher if patients were screened prospectively (7.7–14.6%) [196, 197]. In the last few years, an increased number of incidental diagnosis was evident in normotensive and asymptomatic patients due to the large use of advanced imaging and a better knowledge of the disease genetic basis. Individuals with PHEOs/PGLs associated with NF1 were predominantly women in the fourth decade of life with no family history of PHEOs/PGLs.

The mean age was younger in NF1 than in patients with sporadic PHEOs/PGLs, while older as compared to patients with other genetic

syndromes, probably due to lack of routine screening for adrenal medulla in NF1 and consequent delayed identification [198, 199].

Approximately 84% of individuals with PHEO/PGL have solitary adrenal tumors, 10% bilateral adrenal tumors, and 6% have extra-adrenal tumors in the abdominal sympathetic chain, the organ of Zuckerkandl or the bladder [200]. Individuals with NF1 are at higher risk of malignant PHEO/PGL than sporadic ones (11.5% vs. 4%) and can present with distant metastases [200]. A recent study found that all cases of bilateral, metastatic, and recurrent PHEOs/PGLs occurred in women [201].

NF1-related PHEOs/PGLs, whether or not secreting, are mostly asymptomatic. When symptomatic, patients can show typical symptoms of catecholamines hypersecretion: hypertension, sweating, palpitations, headache, or flushing.

NF1 PHEOs produce both epinephrine and norepinephrine attributable to the activity of the PNMT enzyme, the terminal enzyme in catecholamine synthesis, which converts norepinephrine to epinephrine [202, 203]. In these patients, the increased plasma and urinary levels of metanephrine (indicating epinephrine overproduction) and normetanephrine (a norepinephrine metabolite) help to discriminate NF1 from VHL tumors that express only a noradrenergic phenotype [202, 203]. All patients with NF1, such as patients with MEN2, presented with tumors characterized by increased plasma concentrations of metanephrines, in contrast plasma-free methoxytyramine was elevated only in 39% of patients with NF1 [203]. Therefore, when suspected, PHEOs are diagnosed by assessing the levels of plasma-free metanephrines and performing abdominal imaging (CT or MRI), combined with functional imaging using ^{123}I-MIBG or ^{18}F-DOPA PET [196].

Clonidine suppression testing can also be used in case of an indeterminate adrenal nodule associated with elevated urinary metanephrine levels [204].

Over the last few years, the potential significance of systematic screening for PHEO/PGL in patients with NF1 has been questioned in the literature. If individuals with other hereditary endocrine neoplasia syndromes are routinely screened for PHEO/PGL, contrarily, both adult and pediatric NF1 guidelines not recommend routine biochemical screening for these types of tumors. They recommend that patients with NF1 should have a specialist clinic visit once a year with blood pressure measurement, given the association with renal artery stenosis and PHEO. According to the American College of Medical Genetics and Genomics, only patients with NF1 and hypertension, aged ≥30 years, who are pregnant, and/or symptomatic should be considered for biochemical or imaging screening. Some recent studies suggest that systematic biochemical screening should be a part of the routine evaluation in patients with NF1, by regular measurements of plasma-free or urinary fractionated metanephrines, starting from early adolescence and repeated every 3 years [198, 205, 206]. Patients with undiagnosed PHEO/PGL are at risk of developing life-threatening cardiovascular complications due to catecholamine crises triggered by tumor manipulation, anesthesia, drugs, pregnancy, or rarely metastatic disease [206], so biochemical testing should also be carried out prior to elective surgical procedures and conception [201, 206].

Surgical resection with laparoscopic adrenalectomy is the standard treatment for these tumors. Posterior retroperitoneoscopic adrenalectomy is a reasonable approach with a more direct access to the adrenal gland in cases with significant history of abdominal surgeries and bilateral adrenal tumors [207]. However, in last years, management of hereditary PHEOs has drastically evolved and cortical sparing adrenal surgery may be proposed to avoid definitive adrenal insufficiency especially in case of bilateral PHEOs with low risk of malignancy, the most great experience was in patients with MEN2 and VHL [208].

Patients with NF1 had the most volatile intraoperative hemodynamic course and more severe postoperative complications that may be related to large tumors associated with abundant catecholamine secretion [202].

The treatment of malignant PHEO should be focused on symptomatic control of the hypersecretion using alpha and beta adrenergic blockade.

If possible, a surgical excision or a debulking procedure should be performed. No effective treatment currently exists for PHEO with distant metastases. Internal radiotherapy with ^{131}I-MIBG and chemotherapy, using cyclophosphamide, vincristine, and dacarbazine, have been widely used with poor responses. Sunitinib, an oral receptor TKI, inhibits catecholamine synthesis and secretion in PHEO tumor cells and may prove to be useful in the treatment of malignant PHEOs in the future even in the context of genetic syndromes [209].

Funding and Acknowledgment This chapter, part of the volume *Neuroendocrine Neoplasia Management*, has been partially supported by a grant of the Italian Ministry of Education, Research and University (PRIN 2017Z3N3YC).

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