Practical Clinical Endocrinology

Peter Igaz
Editor

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ISBN 978-3-030-62010-3 ISBN 978-3-030-62011-0 (eBook)
https://doi.org/10.1007/978-3-030-62011-0

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

Endocrinology is a fascinating field of medicine. It is very versatile and stimulating. Practicing endocrinology promotes our abilities in differential diagnosis and complex thinking.

This book of endocrinology aims to give the reader an overall and deep presentation of contemporary endocrine practice. In order to highlight its practical approach, diseases are presented via endocrine cases where the questions and pitfalls in diagnosis and treatment are discussed similar to real life experiences. Moreover, an unconventional question-answer format is used where the most important features of the diseases are underlined as questions.

As the book focuses on the practice, that is, symptoms, diagnosis, differential diagnosis, and treatment issues related to a wide variety of endocrine diseases, only minimal theory of endocrinology is included wherever it aids comprehension. This book is therefore designed for those who have some basic knowledge in endocrinology.

Practical Clinical Endocrinology is dedicated primarily to adult endocrinology; however, some important endocrine diseases from childhood that are certainly continued to be treated in adults, for example, congenital adrenal hyperplasia, are also discussed.

The book is comprised of seven parts along the most important endocrine organs – Part 1: Diseases of the Pituitary and the Hypothalamus; Part 2: Diseases of the Thyroid; Part 3: Diseases of the Parathyroid and Metabolic Bone Diseases; Part 4: Diseases of the Adrenal; Part 5: Diseases of the Gonads; Part 6: Neuroendocrine Tumors and Paraneoplastic Endocrine Syndromes; and Part 7: Multiple Endocrine Neoplasia Syndromes. There are 52 chapters in the book that aim to cover the most common diseases in endocrinology. Apart from the most important and most common endocrine diseases, many rare but interesting diseases (e.g., hormone resistance syndromes) are also discussed. In addition to chronic diseases that constitute the major part of endocrinology, important emergency conditions and complications such as thyroid storm, adrenal crisis, and the management of hormone-related electrolyte disturbances are also discussed.

The book contains 117 figures and 107 tables to facilitate understanding.

Who can find this book useful? The book is meant for a broad audience, but first of all to medical residents in training and preparing for a board exam in internal medicine and/or endocrinology. Moreover, this book can also be useful for established specialists in endocrinology or internal medicine to deepen or refresh their knowledge. The book can also be interesting to university students, most notably the chapters on common diseases from which exam questions are frequently prepared. Some questions from the book can even be asked and therefore be interesting both for students and examiners.

I do really hope that this book represents a novel way of learning and refreshing our knowledge in endocrinology and the reader will find it interesting.

Last but not least, I would like to thank all the authors for their devotion to make this book, which I hope was worth the efforts.

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Budapest, Hungary
2020

Contents

II Diseases of the Thyroid

III Diseases of the Parathyroid and Metabolic Bone Diseases

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About the Editor

Peter Igaz

is full professor of medicine and endocrinology at the Semmelweis University in Budapest, Hungary. He began working at the 2nd Department of Internal Medicine in 1997 after finishing his medical studies, where he cleared board exams in internal medicine, endocrinology, and clinical genetics. Besides his medical degree, Dr. Igaz has degrees also in molecular biology and law. From July 2016 till May 2020, he was the director of the 2nd Department of Medicine, since 2017 as full professor. Since May 2020, due to the restructuring of Semmelweis University, he is heading the Department of Endocrinology at the Department of Internal Medicine and Oncology.

He was awarded a PhD in 1999 and the Doctor of Sciences title by the Hungarian Academy of Sciences in 2013. His clinical activity in endocrinology is broad, but his primary clinical interests are focused on adrenal diseases, neuroendocrine tumors, and multiple endocrine neoplasia syndromes. Under his leadership, the 2nd Department of Internal Medicine was awarded the title of Center of Excellence by ENETS (European Neuroendocrine Tumor Society) in 2019, and Dr. Igaz serves as a co-head of the center. In research, Dr. Igaz is dealing mainly with genomics, non-coding RNAs, and microRNAs in endocrine (mostly adrenal) tumors. His research group was among the first to describe the microRNA profiles of adrenocortical and adrenomedullary tumors and they identified novel potential markers for diagnosis. Novel pathogenic pathways were also revealed by the genomics studies performed by his group. Dr. Igaz has over 150 scientific papers. Since 2017, he is also heading the Molecular Medicine Research Group of the Hungarian Academy of Sciences and Semmelweis University. Dr. Igaz has supervised seven PhD students to date, and six of them have already been awarded the PhD degree. Prior to editing this book, he edited two books for Springer in the Experientia Supplementum Book Series: *Circulating microRNAs in Disease Diagnostics and Their Biological Relevance* (2015) and, together with Prof. Attila Patócs as co-editor, *Genetics of Endocrine Diseases and Syndromes* (2019).

Abbreviations

5-HIAA	5-hydroxyindolacetic acid
17-OH-progesterone or 17-OHP	17-hydroxyprogesterone
21-OHD	21-hydroxylase deficiency
25-OH-D or 25(OH)D	25 hydroxyvitamin D
A	Adrenaline
A/C	Aldosterone to cortisol ratio in adrenal venous sampling
AC	Atypical carcinoid
ACC	Adrenocortical cancer
ACEI	Angiotensin converting enzyme inhibitor
ACTH	Adrenocorticotropic hormone/adrenocorticotropin
AD	Androstenedione
ADH	Antidiuretic hormone
ADHD	Attention deficit hyperactivity disorder
AE	Androgen excess
AFC	Antral follicle count
AGE	Advanced glycosylation end products
AI	Adrenal incidentaloma
AIP	Aryl hydrocarbon receptor interacting protein
AIS	Androgen insensitivity
AMH	Anti-Müllerian hormone
APA	Aldosterone producing adenoma
APS	Autoimmune polyendocrine syndrome
AR	Androgen receptor
ARB	Angiotensin receptor blocker
ARR	Aldosterone-to-renin ratio
AST	Androgen-secreting tumor
ATA	American Thyroid Association
AVS	Adrenal venous sampling
aTG	Anti-thyroglobulin antibody
aTPO or anti-TPO	Anti thyroid peroxidase antibody
AVP	Arginine vasopressin
AVS	Adrenal venous sampling
AVPR2	Arginine vasopressin type 2 receptor
BA	Bilateral adrenalectomy
BAH	Bilateral adrenal hyperplasia
βHCG	Human chorionic gonadotropin β
BHOB	β-hydroxy-butyrate
BIPSS	Bilateral inferior petrosal sinus sampling
BMAH	Bilateral macronodular adrenal hyperplasia
BMD	Bone mineral density
BMI	Body mass index
BWPS	Burch-Wartofsky point scale

CA	Catecholamine
CaCrCR	Creatinine clearance ratio
CAH	Congenital adrenal hyperplasia
CAIS	Complete androgen insensitivity syndrome
CAPTEM	Capecitabine-temozolomide
CAS	Clinical activity score (for endocrine orbitopathy)
CaSR	Calcium-sensing receptor
CD	Cushing's disease
CECT	Contrast-enhanced computed tomography
COC	Combined oral contraceptive
CgA	Chromogranin A
CNS	Central nervous system
CPA	Cyproterone acetate
CPM	Central pontine myelinolysis
CRH	Corticotropin releasing hormone
CS	Cushing's syndrome
CSF	Cerebrospinal fluid
CSWS	Cerebral salt wasting syndrome
CT	Computed tomography
CYP11B1	Cortisol synthase gene (11β-hydroxylase type 1)
CYP11B2	Aldosterone synthase gene (11β-hydroxylase type 2)
CYP17	17α-hydroxylase/17,20 lyase gene
CYP21A2	21-hydroxylase gene
DA	Dopamine
DDAVP	Desmopressin, desamino-8D-arginine vasopressin
DHEA	Dehydroepiandrosterone
DHEAS	Dehydroepiandrosterone sulfate
DI	Diabetes insipidus
DIDMOAD syndrome	Diabetes insipidus, diabetes mellitus, optic atrophy, deafness
DRC	Direct renin concentration
DSD	Disorder of sex development
DST	Dexamethasone suppression test
DT	Doubling time
DTC	Differentiated thyroid cancer
DXA	Dual-energy X-ray absorptiometry
DXM	Dexamethasone
DxWBS	Diagnostic whole-body scan
E2	Estradiol
EBRT	External beam radiation therapy
ECFV	Extracellular fluid volume
ECL	Enterochromaffin-like
eGFR	Estimated glomerular filtration rate
ENSAT	European Network for the Study of Adrenal Tumors
EO	Endocrine orbitopathy
EPM	Extrapontine myelinolysis
ER	Endoplasmic reticulum
ESE	European Society for Endocrinology

ESR	Erythrocyte sedimentation rate
ETA	European Thyroid Association
ETE	extrathyroidal extension
EUS	Endoscopic ultrasound
^{18}FDG-PET-CT	^{18}Fluoro-deoxyglucose positron emission computed tomography
FGF-23	Fibroblast growth factor-23
FHA	Functional hypothalamic amenorrhea
FHH	Familial hypocalciuric hypercalcemia
FIPA	Familial isolated pituitary adenoma
FNA	Fine needle aspiration
FNAB	Fine needle aspiration biopsy
FNAC	Fine needle aspiration cytology
FRAX	Fracture risk assessment tool
FSG	Fasting serum gastrin
FSH	Follicle stimulating hormone
FT	Free testosterone
fT4	Free T4
fT3	Free T3
FTC	Follicular thyroid cancer
GD	Graves' disease
GDM	Gestational diabetes mellitus
GERD	Gastroesophageal reflux disease
GFR	Glomerular filtration rate
GH	Growth hormone
GHRH	Growth-hormone-releasing hormone
GI	Gastrointestinal
GLP-1	Glucagon-like peptide 1
GnRH	Gonadotropin-releasing hormone
GRS	Glucocorticoid resistance syndrome
HCG	Human chorionic gonadotropin (=human chorionic gonadotropin β)
hGR	Human glucocorticoid receptor
HDDST	High-dose dexamethasone suppression test
HEENT	Head, eyes, ears, nose, and throat examination
HHM	Humoral hypercalcemia of malignancy
HNPGL	Head and neck paragangliomas
HOMA-index	Homeostasis model assessment of insulin resistance
HPA	Hypothalamus–pituitary–adrenal axis
HPT-JT	Hyperparathyroidism-jaw tumor syndrome
HRT	Hormone replacement therapy
HSD11B2	11β-hydroxysteroid dehydrogenase type 2
HU	Hounsfield unit
ICSI	Intracytoplasmatic sperm injection
ICTP	Carboxy-terminal telopeptide of type I collagen
IFN	Interferon
IGF-1	Insulin-like growth factor 1

IL-6	Interleukin-6
IMRT	Intensity-modulated radiotherapy
ITT	Insulin tolerance test
IU	International unit
LBW	Low-birth weight
LH	Luteinizing hormone
LOH	Local osteolytic hypercalcemia
MACS	Mild autonomous cortisol secretion
MAH	Malignancy-associated hypercalcemia
MAIS	Mild androgen insensitivity
MEN	Multiple endocrine neoplasia
MIBI	Methoxyisobutylisonitrile
MN	Metanephrine
MRHE	Mineralocorticoid responsible hyponatremia in the elderly
MRI	Magnetic resonance imaging
MRKH syndrome	Mayer-Rokitansky-Küster-Hauser syndrome
mTOR	Mechanistic target of rapamycin
MTC	Medullary thyroid cancer
NA	Noradrenaline
NAFLD	Non-alcoholic fatty liver disease
NCAH	Non-classical CAH (congenital adrenal hyperplasia)
NEN	Neuroendocrine neoplasm
NET	Neuroendocrine tumor
NFPA	Non-functional pituitary adenoma
NMN	Normetanephrine
NSAID	Non-steroidal anti-inflammatory drug
NSE	Neuron specific enolase
OC	Oral contraceptive
ODS	Osmotic demyelination syndrome
OGTT	Oral glucose tolerance test
PA	Primary aldosteronism
PAC	Plasma aldosterone concentration
PAI	Primary adrenal insufficiency
PAIS	Partial androgen insensitivity
PC	Pulmonary carcinoid
PCOM	Polycystic ovary morphology
PCOS	Polycystic ovary syndrome
PEI	Percutaneous ethanol sclerotherapy
PET-CT	Positron emission tomography – computed tomography
PFS	Progression-free survival
PGGR	Primary generalized glucocorticoid resistance
PHPT	Primary hyperparathyroidism
POI	Primary ovarian insufficiency
POsm	Plasma osmolality

PPGL	Pheochromocytoma/paraganglioma
PPI	Proton pump inhibitor
PPNAD	Primary pigmented nodular adrenal hyperplasia
PPT	Postpartum thyroiditis
PRA	Plasma renin activity
PRRT	Peptide receptor radionuclide therapy
PRL	Prolactin
PTC	Papillary thyroid cancer
PTH	Parathyroid hormone
PTHrP	Parathyroid hormone-related protein
PTU	Propylthiouracil
RAAS	Renin-angiotensin-aldosterone system
RAI	Radioiodine
RAIT	Radioiodine therapy
RANKL	Receptor activator of nuclear factor kappa-beta ligand
RECIST	Response evaluation criteria in solid tumors
REE	Resting energy expenditure
RFA	Radiofrequency ablation
rhTSH	Recombinant human TSH
RT	Radiotherapy
rT3	Reverse triiodothyronine
RTH	Thyroid hormone resistance
SACT	Selective arterial calcium stimulation
SAI	Secondary adrenal insufficiency
SCLC	Small cell lung cancer
SERM	Selective estrogen receptor modulators
SGLT2	Sodium-glucose cotransporter 2
SHBG	Sex hormone binding globulin
SIAD	Syndrome of inappropriate antidiuresis
SIADH	Syndrome of inappropriate ADH secretion
SIRT	Selective internal radiation therapy
SNA^+	Serum Na^+ concentration
SPECT-CT	Single photon emission computed tomography
SRI	Somatostatin receptor imaging
SRS	Stereotactic radiosurgery
SRY	Sex determining region of chromosome Y
SSA	Somatostatin analogue
SSIR	Severe insulin resistant syndromes
SSTR	Somatostatin receptor
SV-CAH	Simple virilizing form of congenital adrenal hyperplasia
SW-CAH	Salt-wasting form of congenital adrenal hyperplasia
SWS	Salt-wasting syndrome
T	Testosterone
T2D	Type 2 diabetes mellitus
T3	Triiodothyronine
T4	Thyroxine

TACE	Transarterial chemoembolization
TART	Testicular adrenal rest tissue
TESE	Testicular extraction of sperm
TBG	Thyroid binding globulin
TC	Typical carcinoid
TFT	Thyroid hormone function test
Tg	Thyroglobulin
TgAb	Anti-thyroglobulin antibody
TGT	Transient gestational thyrotoxicosis
TH	Thyroid hormone
TIRADS	Thyroid imaging reporting and data systems
TIH	Thiazide-induced hyponatremia
TKI	Tyrosine kinase inhibitor
TN	Thyroid nodule
TNM	Tumors nodes metastases
TRAb	TSH (thyrotropin) receptor antibody
TRα	Thyroid hormone receptor alpha
TRβ	Thyroid hormone receptor beta
TRH	Thyrotropin releasing hormone
TRIAC	Triiodothyroacetic acid
TSA	Transsphenoidal adenomectomy
TSH	Thyroid stimulating hormone (thyrotropin)
TSH-oma	TSH-secreting pituitary adenomas
TSS	Transsphenoidal surgery
TT	Total testosterone
UFC	Urinary free cortisol
ULN	Upper limit of normal
UNa^+	Urine sodium concentration
UOsm	Urine usmolality
US	Ultrasound
VHL	Von Hippel-Lindau syndrome
VIP	Vasoactive intestinal peptide
VTE	Venous thromboembolism
VUS	Variant of unknown/uncertain significance
WBS	Whole body scan
XGH	Xanthogranulomatous hypophysitis
ZES	Zollinger-Ellison syndrome

Diseases of the Pituitary and Hypothalamus

The pituitary gland is the master regulator of the endocrine system. The anterior lobe of the pituitary secretes prolactin, growth hormone, and several other very important hormones that regulate major endocrine organs such as the thyroid, adrenal glands, and the gonads. The thyroid, adrenal cortex, and gonads are not capable of hormone secretion on their own, as the stimulating hormones from the pituitary are essential for their functioning. The pituitary, however, is not autonomous either since various factors from the hypothalamus regulate hormone secretion from the anterior pituitary. The regulatory axes for the thyroid, adrenal cortex, and gonads thus include three components, for example, hypothalamic-pituitary-thyroid or hypothalamic-pituitary-adrenal axes. These axes involve negative feedback regulation, that is, the product of the peripheral hormone-producing organ (e.g., cortisol from the adrenal cortex) inhibits the secretion of the respective stimulating hormones from the hypothalamus (corticotropin releasing hormone) and pituitary (adrenocorticotropic hormone).

In contrast to the anterior lobe, the posterior lobe of the pituitary does not produce hormones on its own, but stores the hormones produced by hypothalamic nuclei (antidiuretic hormone and oxytocin).

Based on the three-level regulation of the hypothalamic-pituitary-thyroid/adrenal/gonad axes, hormone deficiency due to the disease of the peripheral hormone-producing organs (thyroid, adrenal cortex, or gonads) is termed primary insufficiency, whereas pituitary and hypothalamic insufficiency are termed secondary and tertiary, respectively.

In this part of the book, the major diseases of the pituitary and hypothalamus are discussed. The first chapters (► Chaps. 1, 2, 3, 4, and 5) present diseases associated with pituitary tumors (and

craniopharyngioma). Pituitary tumors are quite frequent, representing about 10 % of intracranial neoplasms. Both hormone-secreting and non-functioning tumors can have major clinical consequences that are presented in these chapters.

In ► Chaps. 6 and 7, diseases of hormone insufficiency related to the pituitary and hypothalamus are discussed. ► Chapter 8 presents hypophysitis, an inflammatory disease of the pituitary that is gaining increasing clinical importance due to novel anti-cancer therapies (immune checkpoint inhibitors).

The last two chapters of this part discuss the diseases associated with the lack or overproduction of antidiuretic hormone. The management of hyponatremia, which is the most common electrolyte abnormality, is presented in ► Chap. 10.

Contents

Prolactinoma

Beatrix Sármán

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_1

1

Opening

This chapter summarizes the main features of hyperprolactinemia in female and male patients, the diagnostic and differential diagnostic steps, and treatment options. Prolactinoma before and during pregnancy is also discussed shortly.

Definition of the Disease

The hormone prolactin (lactotroph hormone) is produced in the anterior pituitary gland. Hyperprolactinemia means the overproduction of prolactin. Prolactin is a major hormone regulating breast milk production, but it has several other activities, as well. In contrast with other anterior pituitary hormones that are stimulated by releasing hormones from the hypothalamus (e.g., adrenocorticotropin/adrenocorticotropic hormone (ACTH) stimulated by corticotropin-releasing hormone (CRH), thyroid-stimulating hormone (TSH) stimulated by thyrotropin-releasing hormone (TRH)), prolactin is under a tonic suppression by dopamine produced by hypothalamic cells. Lesions of the pituitary stalk, therefore, can result in elevated prolactin levels due to the falling out of the dopamine-mediated inhibition.

Pituitary adenomas are the most common intracranial tumors comprising up to 10% of all intracranial neoplasms. The prevalence of clinically relevant pituitary adenomas is around 80–100/100000. Prolactin-producing pituitary adenoma (prolactinoma) is the most common pituitary adenoma (about 40% of all pituitary tumors) with a prevalence of 10/100000 in males and 30/100000 in females. Non-functioning pituitary adenoma is the second most common pituitary adenoma, whereas the other forms, i.e., GH- and ACTH-producing adenomas, are rare (discussed in the following chapters). (TSH-producing pituitary tumor is extremely rare.)

Prolactinoma is mostly a benign tumor (>98%); however, some rare malignant cases are also known. A pituitary adenoma smaller than 1 cm in diameter is called microadenoma (microprolactinoma), whereas over 1 cm, it is termed macroadenoma (macroprolactinoma). Prolactin is the only pituitary hormone whose serum level may refer to the tumor size. Prolactinoma is the only pituitary tumor whose treatment is primarily medical. Magnetic resonance imaging (MRI) pictures of a normal pituitary gland are presented in ◘ Fig. 1.1, whereas a microadenoma is shown in ◘ Fig. 1.2.

Prolactin inhibits the secretion of hypothalamic gonadotropin-releasing hormone (GnRH) and also that of pituitary gonadotropins (luteinizing hormone (LH), follicle-stimulating hormone (FSH)), and therefore prolactin overproduction can result in low sex steroid levels in both sexes (secondary/hypogonadotropic hypogonadism).

It must be noted that hyperprolactinemia can have many different causes apart from prolactinoma. These are presented in ◘ Table 1.1. One of the most important causes for hyperprolactinemia in clinical practice is related to drugs having dopamine antagonistic properties.

Since the clinical picture of prolactinoma is different in females and males, these will be presented via two different clinical cases.

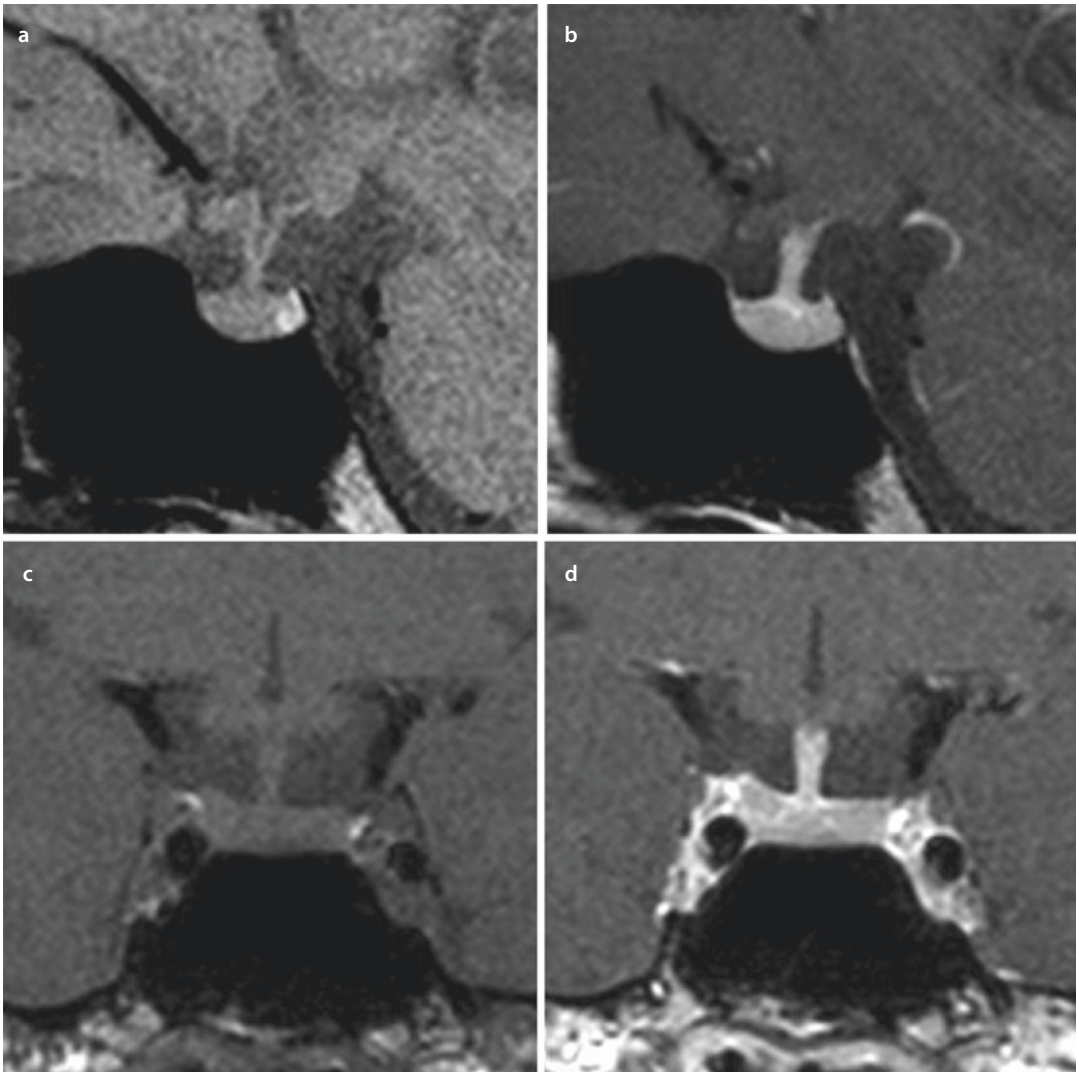

Fig. 1.1 T1-weighed magnetic resonance imaging (MRI) of a normal pituitary. **a** Sagittal, native, **b** sagittal with contrast, **c** coronal native, **d** coronal with contrast. (Courtesy of Dr. György Várallyai)

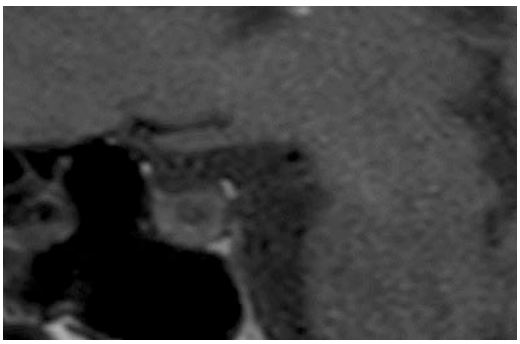

Fig. 1.2 T1-weighed MRI imaging of a pituitary microadenoma, sagittal image

Table 1.1 The most relevant physiological and pathological causes of hyperprolactinemia

	Prolactin serum concentration (ng/mL)
Normal female	<20
Normal male	<10–15
Physiological causes	
During sleeping	<50

(continued)

1

Table 1.1 (continued)

	Prolactin serum concentration (ng/mL)
Pregnancy, breast feeding	
Stress	
Pathological causes[a]	
Microadenoma	<250
Macroadenoma	>500
Pituitary stalk compression	<150
Medication Psychiatric drugs 40–90% (neuroleptics, antidepressants (MAO inhibitor, SSRI, tricyclic and tetracyclic antidepressants) Antihypertensive drugs (verapamil, methyldopa) Histamine 2 receptor blockers Metoclopramide Hormones (estrogen, antiandrogens) Protease inhibitors	<200
Chronic renal or liver failure	
Hypothyroidism	<100
Polycystic ovary syndrome (PCOS)	

Normal levels may be slightly different between laboratories

[a]The prolactin values in pathological conditions represent the usual ranges, but considerable variations can occur

MAO monoamine oxidase, *SSRI* selective serotonin reuptake inhibitor

Case 1 Prolactinoma in Women

A 41-year-old woman was presented to our Department after a neurosurgical intervention (transsphenoidal pituitary surgery). Her medical history included treatment for depression (paroxetine). Medical examination was started because of chronic headache without other neurological symptoms. Her last menstruation cycle was 2 years before the onset of headache, and sometimes she experienced white "milk-like" breast secretion. A sella MRI was performed that described a 1.5 cm large macroadenoma which reached but did not compress the optic chiasm. Histology of the removed tumor confirmed the diagnosis of prolactinoma.

What are the clinical features in this case that are suspicious for a prolactinoma?

The major hormonal effects of hyperprolactinemia are related to the decreased levels of some sex hormones and to galactorrhea (milk production in non-lactating women or very rarely in men). Moreover, pituitary macroadenomas can have mass effects/compression symptoms due to the large size of the tumor.

Clinical symptoms of hyperprolactinemia in premenopausal females:

- Menstrual irregularity: oligo-/amenorrhea – most common symptom
- Infertility
- Galactorrhea – 25–40% of all cases
- Low bone mineral density

Compression symptoms/mass effects with macroadenomas:

In postmenopausal women, these are often the first symptoms, since estrogen levels are already low:

- Headache.
- Impaired vision (visual loss – typically bitemporal hemianopsia, dual vision).
- Signs of hypopituitarism (secondary hypothyroidism, secondary adrenal insufficiency) (see chapter on hypopituitarism (▶ Chap. 6)).
- In severe cases tumors can infiltrate the cavernous sinus leading to cerebral nerve palsies, or even increased intracranial pressure can occur.

In this case, secondary amenorrhea and galactorrhea together with headache should have been an alarming symptom. In 70% of premenopausal females, galactorrhea and oligo-/amenorrhea represent hyperprolactinemia. The symptoms, however, can be much less characteristic in postmenopausal women, and only the macroadenoma-related mass effects could raise suspicion.

What is the definition of secondary amenorrhea?

In women having regular menses, an absence of menstrual cycles for more than 3 months is termed secondary amenorrhea, whereas in women with irregular menses, an absence for more than 6 months is needed. Primary amenorrhea, on the other hand, is defined as no menstrual cycles by the age of 15 years or thereafter.

Due to the intensive headache and tumor size, the patient was immediately presented to a neurosurgeon without prior endocrinological work-up. Was that correct?

No. Prolactinomas, including macroprolactinomas, react very well to medical treatment. Moreover, the patient did not have symptoms of visual impairment, and the MRI showed that the tumor reached, but did not compress, the optic chiasm.

What kind of examinations should be performed in case of a pituitary macroadenoma?

Hormonal work-up:
- Pituitary hormones: gonadotropins (luteinizing hormone (LH), follicle-stimulating hormone (FSH), growth hormone (GH), prolactin, adrenocorticotropin hormone (ACTH), thyroid-stimulating hormone (TSH))
- Other hormones: cortisol, free T4 (fT4), estrogen (female), testosterone (male), IGF-1 (insulin-like growth factor 1)
- Total and macroprolactin measurement (see later)

Other tests:
- Visual field examination
- Osteodensitometry (chronic hypogonadism decreases bone mineral density)
- Liver and kidney function

Unfortunately, there was no hormonal examination prior to the neurosurgical intervention in this case. Which conditions could legitimate urgent surgery?

Urgent neurosurgical intervention is warranted in patients with severe and progressing visual field defects, e.g., threatening vision loss, progressing neurological symptoms, and signs of pituitary apoplexy. Pituitary apoplexy (hemorrhage) can occur in macroadenomas and is usually associated with very intensive headache, visual loss, and neurological symptoms. The hormone results after surgery are presented in Table 1.2.

What can be inferred from these hormone results?

Table 1.2 Hormone results following the neurosurgical intervention

Total prolactin (ng/mL)	1103.75	1.39–24.20
Active prolactin (ng/mL)	729.35	
Macroprolactin (ng/mL)	374.4	
ACTH (pg/mL)	7.5	7.2–63.3
Cortisol (µg/dL)	4.74	8.00–25.00
TSH (mIU/L)	0.2840	0.350–4.940
Free T4 (pmol/L)	11.36	9.00–23.20

(continued)

1

Table 1.2 (continued)

FSH (IU/l)	4.32	2.4–12.6 follicular phase 14.0–95.6 ovulatory phase 1.0–11.4 luteal phase 7.7–58.5 postmenopausal
LH (IU/l)	2.23	3.5–12,5 follicular phase 4.7–21.5 ovulatory phase 1.7–7.7 luteal phase 25.8–134.8 postmenopausal
Estradiol (pg/mL)	23.0	24,5–196 follicular phase 66,1–411 ovulatory phase 40,0–261 luteal phase <10–39,2 postmenopausal

Prolactin level is still high that is not surprising as the removal of macroadenomas is often incomplete. Moreover, TSH is slightly lower, but free T4 is normal. ACTH is in the low range, and the morning cortisol is also low. FSH, LH, and estradiol are also low.

All these hormonal results are suggestive of hypopituitarism, and therefore substitution with hydrocortisone and levothyroxine was started (see chapter on hypopituitarism (▶ Chap. 6)).

The patient took an antidepressant which is known to influence the serum prolactin level. Would you stop or change medication (if possible) before measuring prolactin level?

In this case, no. The antidepressant can elevate prolactin levels, but this is usually markedly less than in this case (usually <100 ng/mL, but much higher values can also be seen in some drug-related cases) (Table 1.1). The size of the pituitary tumor and the typical symptoms are clearly indicative of a pituitary tumor/prolactinoma. The differential diagnostic problem of hyperprolactinemia induced by dopamine agonistic drugs can be significant in case of pituitary microadenomas, where it can be rather difficult to differentiate the origin of hyperprolactinemia if the drug cannot be omitted or changed.

What is macroprolactinemia?

Macroprolactin is a complex of prolactin with immunoglobulin G (IgG) that is biologically inactive, and therefore it does not have pathological significance. The prevalence of macroprolactinemia is 10–25% in patients with hyperprolactinemia. It is important to exclude macroprolactinemia in all patients with hyperprolactinemia. (Serum samples should be pretreated with polyethylene glycol to precipitate macroprolactin before the immunoassay). If there is only predominant macroprolactinemia without clinical symptoms, no intervention is needed.

What is the Hook effect?

Hook effect is an uncommon laboratory phenomenon where the measured serum prolactin level is relatively low even though the patient has a hormone-secreting macroprolactinoma. Very high levels of serum prolactin might interfere with the antibody-based measurements, and thereby a false-negative result might be obtained. In order to avoid this, prolactin should be measured both in undiluted and diluted (1:100) serum samples in patients with large macroadenomas.

How should the high prolactin level be managed in the patient?

Dopamine agonists are the first choice of treatment in prolactinoma, as these drugs are effective both for normalizing prolactin levels in micro- and macroprolactinoma and for reducing tumor size and thereby mass effects including visual field defects.

Amenorrhea and infertility and galactorrhea are usually resolved with dopamine agonist treatment.

What kind of dopamine agonists are available?

Dopamine agonists

Cabergoline is recommended to be the first choice in therapy. Its initial dose is usually 0.25–0.5 mg twice a week. Side effects are rare, but nausea and orthostatic hypotension can occur as with other dopamine agonists. High-dose cabergoline in Parkinson disease was associated with valvulopathy, but it is unclear whether such a risk exists with the much lower doses used in prolactinoma. In patients taking cabergoline, regular (annual) echocardiography is nevertheless warranted for the potential thickening of heart valves.

Bromocriptine was the first dopamine agonist introduced for the treatment of prolactinoma. Its average daily dose varies between 2.5 and 10 mg. It should be taken mostly in the evening due to its orthostatic side effects that can be related to nausea and headache. It might also cause constipation. Both cabergoline and bromocriptine are ergot derivatives.

Quinagolide is a non-ergot dopamine agonist. Its average daily dose is 0.075–0.150 mg also mostly given in the evening. Its side effects are like bromocriptine, but rare.

In the presented case, first bromocriptine and then quinagolide was initiated, but the patient had significant nausea with both; therefore treatment was switched to cabergoline. Galactorrhea diminished and then disappeared, and after 1 year of treatment, the patient has a regular menstrual cycle. Prolactin after 6 months of cabergoline treatment was normal (8.58 ng/mL (1.39–24.20)).

How long should dopamine agonist treatment be continued?

Patients usually take dopamine agonists for several years. Discontinuation of dopamine agonist should be considered only after at least 1 year with stably normal prolactin levels. Even in that case, the dose of dopamine agonist should be tapered very slowly, and prolactin should be regularly monitored (e.g., every 3 months). In cases where the initial tumor size was over 2 cm diameter, discontinuation of dopamine agonist is not suggested.

When should MRI after neurosurgery be first performed?

MRI is usually performed not earlier than 3–6 months after a neurosurgical intervention, since it can be difficult to assess pituitary morphology shortly after the operation.

How often should MRI control performed in patients receiving dopamine-agonist treatment?

MRI controls are usually performed annually.

What are the indications for non-urgent surgery in prolactinoma?

In rare cases, macroprolactinomas do not react to dopamine agonist therapy or the patient is intolerant to dopamine agonists. Some patients choose surgery instead of medical treatment.

Are there other treatment options available for macroprolactinoma?

Radiotherapy (or stereotactic radiosurgery) can be performed in patients with macroprolactinoma who are resistant to dopamine agonist therapy and surgery was unsuccessful.

What should we do if pregnancy is planned or diagnosed?

Macroprolactinomas might grow during pregnancy. The risk for growth in microprolactinomas is minimal. Even if there are no data on the fetal toxicity of dopa-

mine agonists (bromocriptine appears to be safe), it is advised to discontinue them gradually if pregnancy is confirmed. In women planning pregnancy with a macroprolactinoma, surgery should be considered before pregnancy. Women with macroprolactinoma should have visual field examination every 3 months. MRI is usually not performed during pregnancy. If there are signs of tumor growth, bromocriptine (or even cabergoline) can be given. Patients should be informed to seek urgent medical advice in case of intensive headache or visual impairment. In case of therapy resistant growing macroprolactinoma during pregnancy, surgery can be indicated optimally in the second trimester.

Case 2 Prolactinoma in Men

A 69-year-old man was referred to our endocrine outpatient consultation. He had a history of therapy-resistant hypertension and type 2 diabetes. His medical examination started because of an unbearable headache without any other neurological symptoms. A brain MRI was done, and it showed a pituitary macroadenoma of 3 cm diameter. When he was first referred to our Department, he said that his blood pressure was perfect during the last couple of months, so the doses of his antihypertensive drugs could be lowered; moreover, his blood glucose was also so good that he could stop with the antidiabetic drugs. Medical examination revealed gynecomastia and body hair loss.

Does the patient have any alarming symptoms?

Relative hypotension compared with previous periods and "too good" blood glucose control could be signs of hypopituitarism.

What is the next step?

Visual field control and hormone control. No typical visual impairment was confirmed, but low ACTH and cortisol levels and a high total prolactin level were found (see later).

Would you start treatment of hyperprolactinemia immediately?

No. First active prolactin and macroprolactin levels need to be tested.

His active prolactin level: 525.60 ng/mL. Is it a real hyperprolactinemia or could it be the result of pituitary stalk compression?

Hyperprolactinemia due to pituitary stalk compression is usually under 200 ng/mL, so this is probably a hyperprolactinemia caused by a macroprolactinoma.

What are the symptoms of prolactinoma in men?

Especially in elderly men, prolactinoma might not cause any conspicuous hormonal symptoms. Microprolactinomas in elderly may therefore remain undiagnosed, whereas macroprolactinomas are discovered due to their mass effects.

In younger males, prolactinoma can cause symptoms via secondary (hypogonadotropic) hypogonadism, such as impotence and infertility, erectile dysfunction, and low bone mineral density. Rarely, gynecomastia (benign enlargement of the breast glandular tissue in males) can occur, and extremely rarely galactorrhea can be observed.

What are the clinical features in this case that are suspicious for hyperprolactinemia?

Body hair loss and gynecomastia that are both signs of hypogonadism.

The patient had an unbearable headache and hypopituitarism. Would you do an urgent surgery?

No. Even with severe symptoms, medical therapy is the first choice in patient with macro- and microprolactinoma. However, progressive visual impairment/threatening loss of vision or neurological symptoms can warrant an urgent surgical intervention.

Case Continued

Cabergoline was started in a twice 0.5 mg/week dose. Table 1.3 presents the hormonal findings at diagnosis and during therapy. The initial hormonal results show high prolactin levels that were rapidly normalized by the dopamine agonist therapy. Low ACTH and cortisol, low TSH, and low gonadotropin + testosterone levels indicate hypopituitarism. Substitution with hydrocortisone and levothyroxine was started, but this could be later omitted, and as the hormonal results show almost 3 years later, both the adrenal and thyroid axes have recovered. Testosterone level also returned to normal.

Figure 1.3 shows the results of MRI imaging before and after a year of therapy.

Table 1.3 Hormone levels before and during therapy

Hormone (normal range)	2010 May	2010 July	2010 Sept.	2013 Feb.	2013 May	2013 Sept.
Cortisol (8.0–25.0 µg/dL)	1.0			15.0	10.1	18.0
ACTH (7.2–63.3 pg/mL)	7.3			28.3	28.0	34.4
Total prolactin (1.2–10.7 ng/mL)	1328.2	12.28	4.50	7.18		
Active PRL (ng/mL)	525.60	4.0	1.72	5.54		
Macroprolactin (ng/mL)	802.60	7.44	2.78	1.64		
TSH (0.35–4.94 mIU/L)	0.00			0.513		
fT3 (1.71–3.71 pg/mL)	2.81		2.08			
fT4 (0.70–1.80 ng/dl)	1.41		1.53	1.51		
Testosterone (300.0–800 ng/dL)	6.0					382.0
FSH (1,3–11,8 mIU/mL)	2.1					
LH (1,3–11,8 mIU/mL)	0.4					

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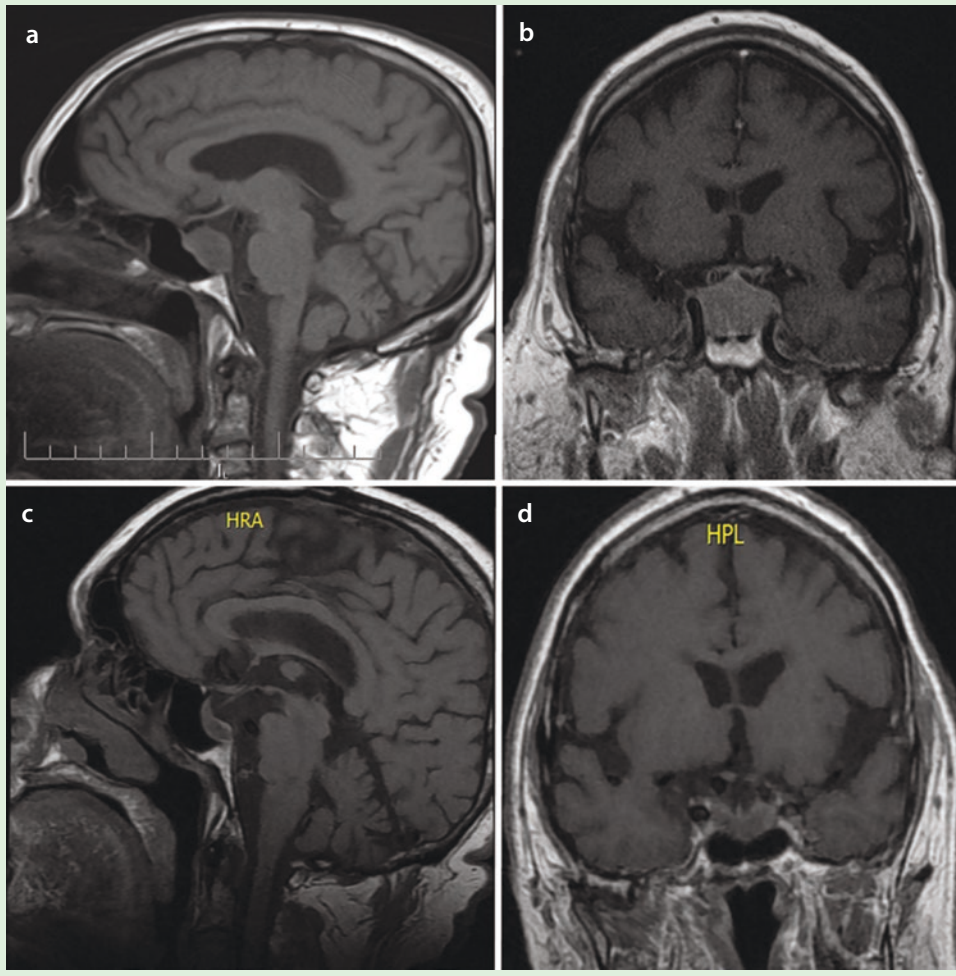

Fig. 1.3 MRI imaging of the macroprolactinoma before (**a** sagittal; **b** coronal) and after (**c** sagittal; **d** coronal) 1 year of treatment with cabergoline (Case 2). The tumor has considerably shrunk after treatment

What are the features of an aggressive pituitary tumor?

Pituitary tumors (including prolactinomas) are mostly slowly growing tumors, and most prolactinomas are responsive to medical treatment. A small subset of tumors, however, is resistant to therapy (including drugs, surgery, or radiotherapy), and there are also recurrences. These aggressive pituitary tumors can infiltrate nearby structures and show a higher proliferative rate on histological analysis (the Ki-67 proliferation marker is higher than 3%).

What is the definition of pituitary cancer?

Pituitary cancer is defined as a pituitary tumor with craniospinal or distant metastases. It is thus not a histological category, but based on the presence of metastases similar to the diagnosis of malignant pheochromocytoma/paraganglioma. Pituitary cancer has a dismal prognosis, but it is fortunately very rare accounting for less than 0.2% of all pituitary tumors.

Tips

The reader is advised to read the following chapters on pituitary tumors (acromegaly (▶ Chap. 2), Cushing's disease (▶ Chap. 3), non-functioning pituitary adenoma (▶ Chap. 4), and hypopituitarism (▶ Chap. 6)).

Take-Home Messages

- Prolactinoma is the most common pituitary adenoma.
- In premenopausal females, symptoms of prolactinoma include oligo-/amenorrhea and galactorrhea, whereas in men signs of hypogonadism (impotence, infertility) are characteristic. Bone mineral density can be decreased in both sexes.
- In both elderly women and men, often the mass effects related to macroprolactinomas are the only signs.
- Macroprolactin levels should be measured in case of hyperprolactinemia.
- Medical history is very important in case of mild hyperprolactinemia.
- Dopamine agonist therapy is the first choice for both micro- and macroprolactinomas.

Suggested Reading

1. Almalki MH, Ur E, Johnson M, Clarke DB, Syed A, Imran SA. Management of Prolactinomas During Pregnancy -- A Survey of Four Canadian Provinces. Clin Invest Med. 2012;35(2):E96–104. https://doi.org/10.25011/cim.v35i2.16293.
2. Capozzi A, Scambia G, Pontecorvi A, Lello S. Hyperprolactinemia: pathophysiology and therapeutic approach. Gynecol Endocrinol. 2015;31(7):506–10. https://doi.org/10.3109/09513590.2015.1017810.
3. Grigg J, Worsley R, Thew C, Gurvich C, Thomas N, Kulkarni J. Antipsychotic-induced hyperprolactinemia: synthesis of world-wide guidelines and integrated recommendations for assessment, management and future research. Psychopharmacology (Berl). 2017;234(22):3279–97. https://doi.org/10.1007/s00213-017-4730-6.
4. Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, Wass JA. Diagnosis and treatment of hyperprolactinemia: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(2):273–88. https://doi.org/10.1210/jc.2010-1692.
5. Molitch ME. Endocrinology in pregnancy: management of the pregnant patient with a prolactinoma. Eur J Endocrinol. 2015;172(5):R 205–13. https://doi.org/10.1530/EJE-14-0848.
6. Raverot G, Burman P, McCormack A, Heaney A, Petersenn S, Popovic V, Trouillas J, Dekkers OM. European Society of Endocrinology Clinical Practice Guidelines for the management of aggressive pituitary tumors and carcinomas. Eur J Endocrinol. 2018;178(1):G1–G24. https://doi.org/10.1530/EJE-17-0796.
7. Shimatsu A, Hattori N. Macroprolactinemia: diagnostic, clinical, and pathogenic significance. Clin Dev Immunol. 2012;2012:167132. https://doi.org/10.1155/2012/167132.

Acromegaly

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Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_2

2

Opening

Acromegaly belongs to the family of rare diseases. Its clinical and biochemical features are unique. The excessive growth hormone production and the consequent rise of insulin-like growth factor 1 lead to the typical acromegalic characteristics. Increased growth hormone activity is associated with increased mortality and decreased quality of life due to several comorbidities; therefore the treatment and the management of the disease are challenging.

Definition of the Disease

Acromegaly is characterized by excessive growth hormone (GH) production and consequent elevation of insulin-like growth factor 1 (IGF-1) levels. Excessive GH production after the closure of the epiphyseal growth plates is termed acromegaly, whereas GH excess before the closure of growth plates leading to a general overgrowth syndrome is termed gigantism. Acromegaly and gigantism are therefore diseases of the same spectrum, but the former develops in adults, whereas gigantism has its onset before puberty. The cause of GH excess is a GH-producing pituitary adenoma (somatotropinoma or GH and prolactin co-secreting mammosomatotropinoma) in the overwhelming majority of cases (>95%). Acromegaly is a rare disease with a prevalence between 2.8 and 13.7/100.000 and with the annual incidence between 0.2 and 1.1 cases/100.000 people. In most studies, there is an equal distribution of prevalence between males and females.

In very rare cases, acromegaly is due to ectopic (paraneoplastic) secretion of GH or growth hormone-releasing hormone (GHRH) responsible for pituitary hyperplasia. The pituitary micro- or macroadenoma (>10 mm) leading to acromegaly/gigantism can occur sporadically or rarely in a familial setting. Familial isolated pituitary adenoma (FIPA) syndrome is the most common familial cause of acromegaly, and the syndromic familial acromegaly [Carney complex, multiple endocrine neoplasia types 1 and 4 (MEN1 and MEN4), and succinate dehydrogenase (SDH)-related syndromes] is less common. The exact genetic basis of the FIPA cases is currently not fully known. One fifth of the FIPA families have germline mutations in the *aryl hydrocarbon receptor-interacting protein (AIP)* gene. Pituitary tumors in FIPA have earlier disease onset and are diagnosed in a younger age than their sporadic counterparts, and the tumor is usually large and invasive.

The chronic GH and IGF-1 elevation results in progressive somatic disfigurement (mainly involving the face and extremities). IGF-1 is mainly produced by the liver, and it is responsible for most symptoms of acromegaly. Due to covert onset and slow progression, acromegaly is often diagnosed even more than 10 years after its onset. This can explain the existence of comorbidities at the diagnosis. Cardiovascular, metabolic, respiratory, neoplastic, endocrine, articular, and bone complications (detailed in ◘ Table 2.1) play crucial roles in increasing mortality rates and decreased quality of life.

Several treatment modalities are available. Effective control of GH and IGF-1 hypersecretion and ablation or stabilization of the pituitary tumor mass leads to improved comorbidities and enhances life expectancy and quality of life. Therefore the early diagnosis of the disease is critical.

Table 2.1 Major clinical symptoms of acromegaly

Local tumor effects	Headache
	Impaired vision
	Cranial nerve palsy
	Hypopituitarism
Musculoskeletal and soft tissue effects	Enlarged hands and feet
	Enlarged tongue and organs
	Oily, thickened skin
	Excessive sweating and body odor
	Skin tags
	Fatigue and muscle weakness
	Joint pain and limited mobility
	Prognathism
	Carpal tunnel syndrome
Cardiovascular effects	Left ventricular hypertrophy
	Arrhythmias
	Hypertension
	Cardiomyopathy
	Congestive heart failure
Pulmonary effects	Sleep apnea
	Severe snoring (obstruction of the upper airway)
	Deepened voice (enlarged vocal cords and sinuses)
Neoplasia	Colon polyp/carcinoma
Endocrine and metabolic effects	Menstrual cycle irregularities in women
	Erectile dysfunction in men
	Insulin resistance and hyperinsulinemia
	Impaired glucose tolerance
	Diabetes mellitus
	Hypertriglyceridemia
	Hypercalciuria
	Goiter

Case Presentation

A 36-year-old man was admitted to our outpatient clinic because of clinical features of acromegaly. His medical history included surgery of the right ear, temporal arteritis, and kidney stones. He had overweight with a body mass index of 38 kg/m^2. His main complaints were the change of his face and increase of the size of his hands and feet.

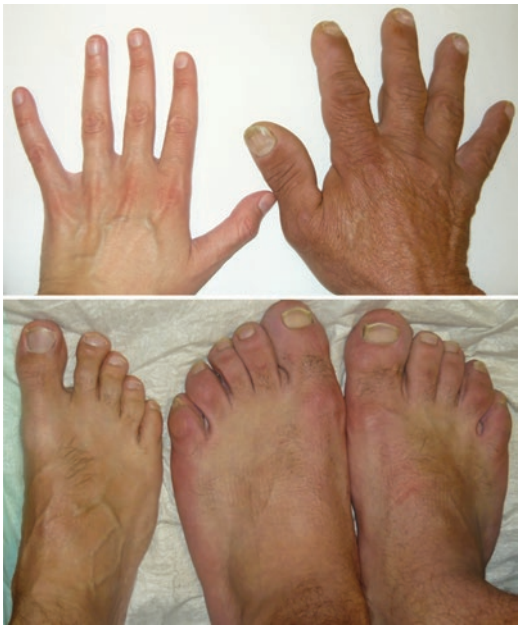

Fig. 2.1 Hand and feet of an acromegalic patient (right) [compared to normal (left)]. (Courtesy of Professor Miklós Góth)

What are the typical clinical features of acromegaly?

Common signs of acromegaly are enlarged hands and feet (Fig. 2.1). Patients recognize that their shoes/gloves don't fit any more or they are not able to put on or pull off their rings (sausage finger). There are typical changes of the face, such as enlarged nose and lips, wider space between the teeth, and protruding lower jaw (as seen on Fig. 2.2). Enlarged tongue (macroglossia) is also often observed. Patients often complain about sweating, and voice

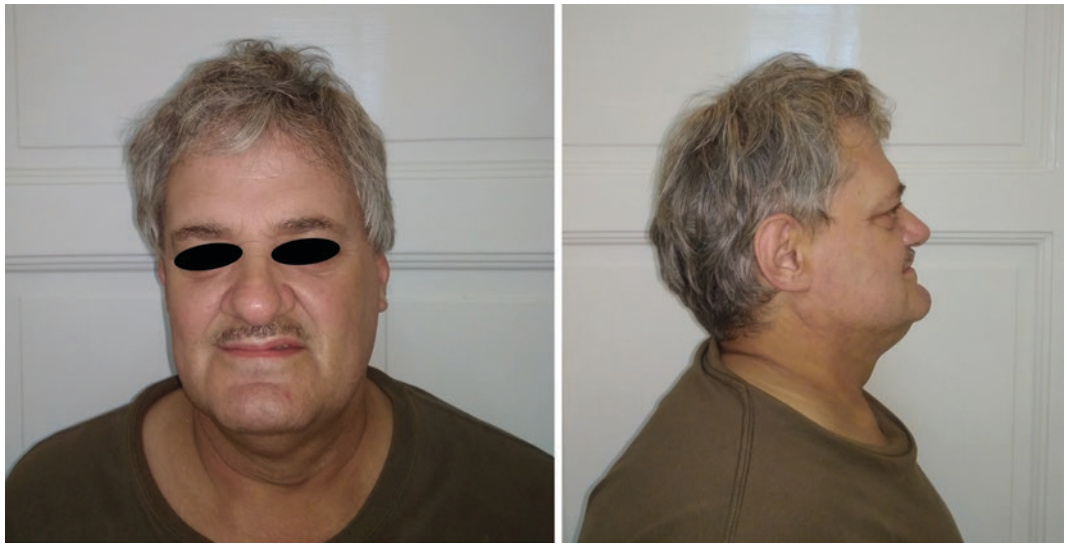

Fig. 2.2 The face of our acromegalic patient

deepening may also occur. These features develop very slowly; therefore the diagnosis might be established with 7–10-year delay from the initial symptoms. The phenotypic changes are often not noticed by the patient and her/his family, but by a new acquaintance, e.g., a new general practitioner. Dentists might also raise the suspicion for acromegaly.

There are also typical medical conditions, which are associated with acromegaly. Our patient had kidney stones, which are seen in 8–10% of the cases, while hypercalciuria is more frequent (80%). The main comorbidities associated with acromegaly are the following: high blood pressure, arrhythmias, left ventricular hypertrophy, impaired glucose tolerance or diabetes mellitus, sleep apnea, and carpal tunnel syndrome. Visceromegaly can also occur affecting the heart, thyroid, liver, kidney, lung, etc.

If acromegaly is caused by a growth hormone-secreting pituitary macroadenoma, there can be mass effects related to the tumor, such as headache, visual disturbances, and hypopituitarism.

The major clinical symptoms of acromegaly are summarized in Table 2.1.

How to proceed with the diagnosis?

The main goal of the diagnostic steps is to verify the GH and IGF-1 overproduction and to find the source of the GH excess.

Biochemical measurements include GH and (age- and gender-matched) IGF-1 levels, which were both elevated in our patient (GH: 30.3 ng/ml, normal range 0–5 ng/ml, IGF-1: 1668 ng/ml, 4.55× upper limit of normal (ULN), age-matched IGF-1 normal range 137–366 ng/ml). However, random GH measurement is not the gold standard for the diagnosis of acromegaly, as serum levels may fluctuate from undetectable to high levels because of its episodic secretion. GH level measurement during a 75 g oral glucose tolerance test (OGTT) is required for the diagnosis. In healthy subjects, GH levels fall after glucose administration, while in acromegalic patients, this suppressive effect is missing. A GH nadir ≥1 ng/ml (or ≥0.4 ng/ml using a highly sensitive GH assay) during OGTT-GH suppression test is diagnostic for acromegaly.

The majority of patients with acromegaly have a GH-secreting pituitary adenoma. Magnetic resonance imaging (MRI) should be performed to find a pituitary adenoma and to visualize its extension (Fig. 2.3). Our patient had a large pituitary macroadenoma with a maximum

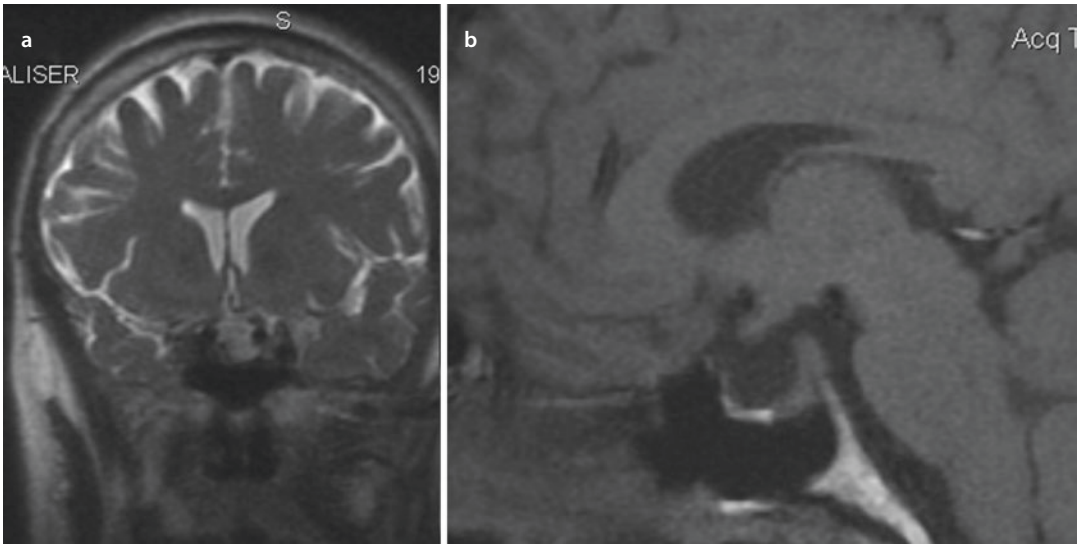

Fig. 2.3 Postoperative MRI of the pituitary adenoma (**a** coronal, **b** sagittal)

diameter of 20 mm. 70–75% of pituitary tumors in acromegaly are macroadenomas, with frequent extension in parasellar or suprasellar regions.

In very rare cases, GH-secreting pituitary carcinoma, a hypothalamic GHRH-secreting tumor, or ectopic GH/GHRH secretion might be the cause of acromegaly. In those cases MRI, chest, and abdominal CT scanning might help to find the tumor.

Which hormone test can be used for screening for acromegaly?

IGF-1 should be first measured in patients who are suspected to suffer from acromegaly. If IGF-1 is normal, the chance for acromegaly is very low.

Should any other endocrine laboratory tests be performed?

Pituitary tumors might cause hypopituitarism by compression on the surrounding normal pituitary tissue, and therefore the evaluation of residual pituitary function is essential. The following hormone levels should be measured: basal prolactin (PRL), FSH, LH, TSH, fT4, fT3, estradiol (in women), testosterone (in men), and cortisol levels. Prolactin levels might be elevated because of pituitary stalk compression by the tumor (so the inhibitory effect of hypothalamic dopamine is prevented) or because of co-secretion of GH and PRL by the pituitary adenoma.

What are the long-term dangers of acromegaly?

Mortality rate is enhanced in acromegaly mainly due to cardiovascular disease, respiratory disorders, and dysregulated glucose metabolism. Diabetes mellitus occurs in about 20% of patients, while hypertension is present in almost half of the patients. Musculoskeletal disorders and arthropathy pain are important complications, which affect negatively the quality of life.

Screening for which kind of diseases/manifestations should be performed in active acromegaly patients?

Active acromegalic patients should be screened for cardiovascular complications (hypertension, arrhythmia, cardiomyopathy), endocrine and metabolic disorders (e.g., hypopituitarism, glucose metabolism impairment), sleep apnea,

musculoskeletal disorders (e.g., vertebral fracture), and colon polyps/cancer.

2

Is the risk for tumors increased in acromegaly?

The incidence of colon and thyroid cancer appears to be elevated in acromegaly. Therefore screening colonoscopy should be performed at diagnosis and then repeated depending on the result, the family history, and disease activity. Thyroid ultrasound is suggested for those patients with palpable nodule or increased risk for thyroid cancer.

What are the major death causes in acromegaly patients?

The leading cause of death is cardiovascular disease, followed by respiratory and cerebrovascular disease.

What kinds of treatment options are available in acromegaly?

The main aims of treatment are to reduce mortality by achieving biochemical control (age- and gender-matched normalized IGF-1 levels and controlled GH levels) and to reduce tumor mass.

Current therapeutic options are surgery, medical treatment, and radiotherapy (Table 2.2). The suggested therapeutic steps are shown in Fig. 2.4.

Table 2.2 Therapeutic modalities in acromegaly

Surgery	Transsphenoidal or transcranial approach
Medical therapy	Dopamine agonists
	Somatostatin analogues
	Growth hormone receptor antagonist
Radiation therapy	Conventional radiotherapy/ stereotactic radiosurgery

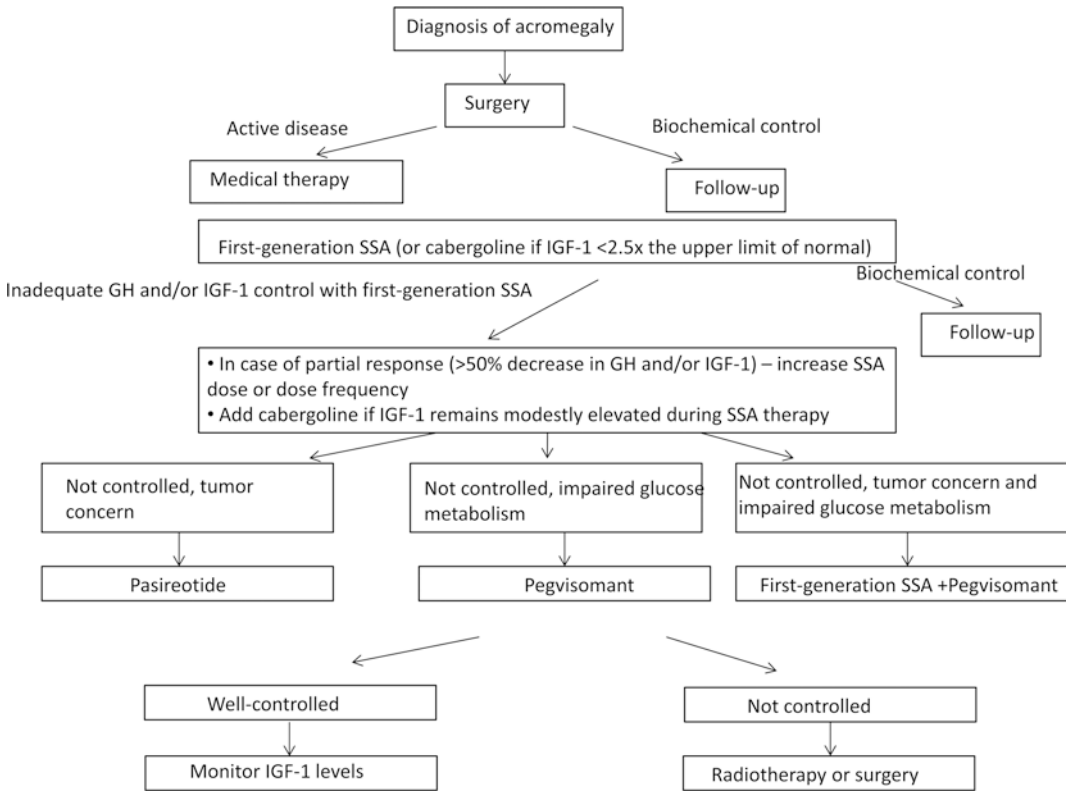

Fig. 2.4 Therapy of acromegaly. (Based on the guideline of Melmed et al. 2018)

The first choice is *surgical treatment* if there are no contraindications (such as severe heart failure or respiratory disease, cases where there is no chance of total resection of the tumor and it doesn't affect vital structures, or when the patient refuses surgery). The operation should be performed in a specialized neurosurgical center. The success of surgical intervention is 30% in case of macroadenomas and 65% in case of microadenomas. Transsphenoidal approach is mainly used in pituitary surgery, but sometimes transcranial resection is necessary.

Our patient had a transsphenoidal pituitary surgery in 2002.

How to evaluate the result of surgical treatment?

Right after a successful surgical intervention, GH levels fall, and metabolic dysfunction and soft tissue swelling begin to improve. Clinical and biochemical evaluation should be performed 12 weeks after surgery by measuring IGF-1, random GH, and GH levels during OGTT. Our patient didn't achieve biochemical control, as seen in Table 2.3, with a GH nadir of 8.8 ng/ml during OGTT [cutoff is the same as for diagnosis; ≥1 ng/ml (or ≥0.4 ng/ml using a highly sensitive GH assay) shows active disease].

What are the potential complications of surgery?

Experienced neurosurgeons have better complication rates. The main side effects of surgery might be newly developed hypopituitarism, permanent diabetes insipidus, hemorrhage, meningitis, or cerebrospinal fluid leak. Experienced neurosurgeons have better complication rates.

Table 2.3 Results of the postoperative oral glucose tolerance test in our case

Time point (min.)	0	30	60	90	120
GH level (ng/mL)	13.9	11.1	10.7	9.3	8.8

What is the next step if acromegaly persists after surgery?

The next therapeutic option is medical therapy. There are different types of medicaments used in acromegaly: dopamine agonists, somatostatin analogues (SSAs) and GH receptor antagonist or combination therapy. First-line medical therapy is dopamine agonists and first-generation SSA.

Dopamine agonists (bromocriptine, quinagolide, and cabergoline) are used either as monotherapy or in combination therapy. The most effective with the best side effect profile is cabergoline. Its benefits are mostly seen in patients with mildly elevated IGF-1 level and in tumors co-secreting GH with prolactin.

First-generation SSAs are octreotide and lanreotide. Their long-acting forms are administered once monthly [octreotide long-acting release (LAR) intramuscularly, while lanreotide Autogel subcutaneously]. The standard doses are 10–30 mg/4 weeks for octreotide LAR and 60, 90, or 120 mg/4 weeks for lanreotide Autogel. GH-producing adenomas express four of the five somatostatin receptor (SSTR) subtypes (SSTR1, SSTR2, SSTR3, SSTR5). Octreotide and lanreotide bind predominantly to SSTR2 and less actively to SSTR5. First-generation SSAs reduce tumor mass, and in 25–55% of cases, biochemical control can be achieved. The efficacy of first-generation SSA treatment is determined by pretreatment GH levels, tumor expression of SSTR2, presence of mutation in the AIP gene mutation, tumor granularity (sparsely granulated tumors are less responsive than densely granulated ones), and intensity on MRI (hypointense T2-weighted tumors on MRI respond better to SSA treatment).

SSA therapy can be applied either after surgery to achieve biochemical control, or also preoperatively to reduce complica-

tions of surgery, or after radiotherapy until its effect starts to develop.

SSAs are safe and well tolerated, with mainly gastrointestinal side effects and gallbladder sludge or stones.

Our patient received bromocriptine therapy; then octreotide LAR 20 mg/4 weeks was applied. As it was not effective, its dose was increased to 30 mg/4 weeks.

How to evaluate biochemical control during first-line medical therapy?

The IGF-1 level and the average of multiple GH levels should be measured.

On a 5-point daily GH curve, our patient's average GH level was 19.5 ng/ml (biochemical control means <1 ng/ml), and the IGF-1 level was 968 ng/ml (2.6× ULN). As the MRI showed an intra- and parasellar residual tumor and his acromegaly was still active (and that time no other medical therapeutic options were available), he had a second transsphenoidal surgery in 2004.

The postoperative control showed active disease, with a residual tumor mass, so octreotide LAR 30 mg/4 weeks was given back to him. The control during SSA therapy showed a high GH level (average 40.08 ng/ml) and elevated IGF-1 level (794 ng/ml, 2.1× ULN), and the neurosurgeon didn't advise reoperation, so radiotherapy was performed (with 40 Gy in split doses of 2 Gy fractions).

What can be done if acromegaly is still not well-controlled after surgery and the maximal dose of first-line medical therapy?

There are nowadays many more therapeutic options if disease control is not achieved with surgery, radiotherapy, and first-line medical therapy.

Second-line approaches include the second-generation SSA pasireotide and the GH receptor antagonist pegvisomant.

Pasireotide is a SSA, which binds to all of the SSTRs except for SSTR4. In approximately half of the patients treated with pasireotide, biochemical control can be achieved.

The *GH receptor antagonist* pegvisomant inhibits postreceptor GH signaling and thereby blocks IGF-1 production. It blocks peripheral GH action but has no effect on the pituitary tumor. In 60–90% of patients, pegvisomant normalizes IGF-1 levels. It can be administered as a daily subcutaneous injection in monotherapy, or in combination with first-generation SSAs (in the latter case, 1–2 times weekly administration might be enough). Liver enzymes should be screened during therapy, as elevated hepatic transaminases are one of the main side effects of pegvisomant. The other important side effect is lipodystrophy on local injection site.

As seen on Fig. 2.4, if there is clinically relevant residual tumor and/or clinical concern of tumor growth, pasireotide is advised as second-line medical treatment. As pegvisomant enhances insulin sensitivity (and pasireotide deteriorates glucose metabolism in the majority of cases), GH receptor antagonist is the choice for those with impaired glucose metabolism.

What is the main side effect of pasireotide?

70% of the patients on pasireotide LAR treatment exhibit hyperglycemia, which is the most important side effect of this drug. Pasireotide impairs glucose homeostasis by reducing insulin and incretin secretion. Pasireotide binds with highest affinity to SSTR5; therefore it inhibits more effectively the secretion of insulin (via SSTR5) than that of glucagon (via SSTR2). Patients on pasireotide LAR therapy (or those considered for treatment with it) should be carefully monitored for impaired glucose tolerance or diabetes mellitus.

What is the role for radiotherapy in acromegaly?

Radiotherapy is usually third-line therapy for those patients not controlled by surgery and/or medical therapy. It can be

performed either by conventional external radiotherapy or stereotactic radiosurgery. Radiation arrests tumor growth and ultimately causes tumor shrinkage.

How fast do the effects of radiotherapy appear?

GH and IGF-1 levels start to fall after radiation therapy, but maximal effect starts to develop only after approximately 5–10 years. In the meantime additional medical treatment might be needed.

What can be the side effects of radiotherapy?

Side effects include hypopituitarism, second brain tumor, visual deterioration, and cranial nerve palsies.

How to evaluate disease control during second-line medical therapy?

Regarding the second-generation SSA pasireotide, the method is the same as for first-generation SSAs.

As the GH receptor antagonist prevents peripheral GH action, the GH levels remain elevated, so in the case of pegvisomant, there is no point to measure GH levels; only IGF-1 levels are informative.

What could be the next steps in our patient's case?

To summarize, our patient had a pituitary surgery, followed by medical therapy with dopamine agonist and first-generation SSA. As acromegaly was still active (and that time second-line medical therapy was not available), he had a second pituitary surgery and radiotherapy. Afterward as acromegaly was still active on maximal dose of first-generation SSA, and as the GH receptor antagonist became available, we started pegvisomant therapy in 2006 (in 10 mg/day for 2 months, than 15 mg/day dose). The control IGF-1 level showed reduction after 2 months, and then with higher pegvisomant dose, IGF-1 level normalized (252 ng/ml, 0.68× ULN).

He was controlled on pegvisomant therapy until 2012; however, because of elevating IGF-1 levels, he needed higher doses of pegvisomant. Despite the maximum dose of pegvisomant, his IGF-1 levels increased (maximum 490.6 ng/ml, 1.33× ULN); therefore the first-generation SSA lanreotide Autogel was added to his therapy, in 120 mg/6 weeks and then in 120 mg/4 weeks dose.

Taking into consideration the slightly elevating IGF-1 levels, his residual tumor mass, his normal glucose metabolism, and patient compliance, we decided in 2017 to change his combination therapy to the second-generation SSA, pasireotide monotherapy. We started with 60 mg/4 weeks dose, which resulted in biochemical control of acromegaly (last follow-up visit results: IGF-1129 ng/ml, 0.49x ULN, 5-point daily GH curve average 0.69 ng/ml).

Can acromegaly be inherited?

Very rarely, acromegaly can be inherited as part of endocrine tumor syndromes, such as multiple endocrine neoplasia types 1 and 4 (MEN1, MEN4), Carney complex, or FIPA and SDH-related syndromes.

Tips

The reader is advised to read the preceding chapter on prolactinoma (▶ Chap. 1) and the next chapters on pituitary tumors (Cushing's disease, ▶ Chap. 3) and non-functional pituitary adenoma (▶ Chap. 4). The chapter on hypopitutiarism (▶ Chap. 6) and the chapter on multiple endocrine neoplasia type 1 (▶ Chap. 50) might also be interesting to the reader.

2

Take-Home Messages

- Acromegaly is a rare condition with increased morbidity and mortality.
- Its diagnosis is usually delayed with approximately 3–10 years from initial symptoms.
- Acral enlargement, cardiovascular and respiratory complications, arthropathy, and neuropathy are the main clinical features.
- It is important to screen for additional medical conditions, such as sleep apnea, colorectal polyps/carcinoma, and impaired glucose metabolism.
- The diagnosis is based on elevated IGF-1 levels and lack of suppression of GH during a 75 g oral glucose tolerance test [GH nadir ≥1 ng/ml (or ≥0.4 ng/ml using highly sensitive GH assay)].
- The vast majority of cases are caused by a GH-secreting pituitary adenoma. The best imaging tool is pituitary MRI.
- Therapeutic options for acromegaly include surgery, medical therapy, and radiotherapy.
- Surgery is the first choice if there are no contraindications. Biochemical result of surgery should be evaluated by (age- and gender-matched) IGF-1 levels and GH levels during OGTT.
- Medical therapy includes dopamine agonists, first- and second-generation somatostatin analogues, and GH receptor antagonist.
- Radiotherapy is usually third-line therapy. Biochemical response takes several years to develop.
- Biochemical control during SSA therapy should be IGF-1 level and random/average GH-level measurement. The GH receptor antagonist pegvisomant therapy should be monitored with IGF-1 levels.

Suggested Reading

1. Coopmans EC, Muhammad A, van der Lely AJ, Janssen JAMJL, Neggers SJCMM. How to position pasireotide LAR treatment in acromegaly. J Clin Endocrinol Metab. 2019;104(6):1978–88. https://doi.org/10.1210/jc.2018-01979.
2. Giustina A, Chanson P, Bronstein MD, Klibanski A, Lamberts S, Casanueva FF, Trainer P, Ghigo E, Ho K, Melmed S, Acromegaly Consensus Group. A consensus on criteria for cure of acromegaly. J Clin Endocrinol Metab. 2010;95(7):3141–8. https://doi.org/10.1210/jc.2009-2670.
3. Giustina A, Barkan A, Beckers A, Biermasz N, Biller BMK, Boguszewski C, Bolanowski M, Bonert V, Bronstein MD, Casanueva FF, Clemmons D, Colao A, Ferone D, Fleseriu M, Frara S, Gadelha MR, Ghigo E, Gurnell M, Heaney AP, Ho K, Ioachimescu A, Katznelson L, Kelestimur F, Kopchick J, Krsek M, Lamberts S, Losa M, Luger A, Maffei P, Marazuela M, Mazziotti G, Mercado M, Mortini P, Neggers S, Pereira AM, Petersenn S, Puig-Domingo M, Salvatori R, Shimon I, Strasburger C, Tsagarakis S, van der Lely AJ, Wass J, Zatelli MC, Melmed S. A consensus on the diagnosis and treatment of acromegaly comorbidities: an update. J Clin Endocrinol Metab. 2020;105(4):e937–46. https://doi.org/10.1210/clinem/dgz096.
4. Katznelson L, Laws ER Jr, Melmed S, Molitch ME, Murad MH, Utz A, Wass JAH, Endocrine Society. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(11):3933–51. https://doi.org/10.1210/jc.2014-2700.
5. Melmed S. Acromegaly pathogenesis and treatment. J Clin Invest. 2009;119(11):3189–202. https://doi.org/10.1172/JCI39375.
6. Melmed S, Kleinberg D. Pituitary masses and tumors. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors. Williams textbook of endocrinology. 13th ed; 2016. Elsevier, Philadelphia. p. 268–87.
7. Melmed S, Bronstein MD, Chanson P, Klibanski A, Casanueva FF, Wass JAH, Strasburger CJ, Luger A, Clemmons DR, Giustina A. A consensus statement on acromegaly therapeutic outcomes. Nat Rev Endocrinol. 2018;14(9):552–61. https://doi.org/10.1038/s41574-018-0058-5.

Cushing's Disease

Sabina Zacharieva and Ivayla Uzunova

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_3

Opening

This chapter discusses Cushing's disease, the form of hypercortisolism related to pituitary ACTH oversecretion, its signs and symptoms, diagnosis, differential diagnosis, and treatment options.

3

Definition of the Disease

Cushing's disease (CD) was described by Harvey Cushing in 1912 in his book *The Pituitary Body and its Disorders*. It is the most common cause of endogenous hypercortisolism accounting for approximately 60–80% of the cases. The term Cushing's syndrome (CS) comprises all forms of endogenous hypercortisolism including CD, but also adrenal and ectopic forms that are discussed in separate chapters of the book (► Chap. 27 on adrenal CS and ► Chap. 45 on ectopic hypercortisolism). CD is caused by excessive secretion of adrenocorticotropic hormone (ACTH) by pituitary corticotroph adenomas. These are usually microadenomas, which do not cause symptoms by local mass effect. Macroadenomas are uncommon in patients with CD, but these tumors cause mass effect when their size exceeds 15 mm in diameter. Somatic mutations in the *USP8* gene encoding the ubiquitin-specific protease 8 have been detected recently as the most common alterations in patients with CD (found in 31–63% of corticotroph adenomas). Corticotropinomas secrete excessive amounts of ACTH with increased pulse amplitude and altered circadian rhythm. The partially autonomous ACTH hypersecretion leads to overproduction of cortisol from the adrenal cortex. However, the ensuing hypercortisolism does not suppress ACTH release from adenomatous corticotrophs (as opposed to the negative feedback expected between the adrenal cortex and the normal corticotroph cells), creating a vicious cycle of sustained cortisol oversecretion. A common effect of elevated ACTH levels is bilateral adrenocortical hyperplasia, which may be diffuse or nodular. The prevalence of CD is estimated to be nearly 40 per million, and the incidence ranges from 1.2 to 2.4 per million per year. CD affects women three times more frequently than men, and symptoms commonly appear between the third and the sixth decade of life. It has been reported that CD appears at a younger age with a more severe clinical presentation in men than in women. In older adults, no difference in the prevalence of CD between men and women has been reported.

The most common form of hypercortisolism is, however, the iatrogenic Cushing's syndrome that is caused by exogenous administration of glucocorticoids exploited for their widespread biological activity (e.g., immunosuppressive, oncological use). Iatrogenic CS is often very severe.

Case Presentation

The patient was a young woman at the age of 26, who was referred to our clinic. She had complaints for 3 years. At first her menstruation had become irregular with episodes of amenorrhea. In the next few years, she started to gain weight and noticed that she got bruised more easily, and her facial hair growth increased.

Physical examination revealed centripetal obesity with a BMI level of 32 kg/m^2; a moon face with facial plethora; facial hirsutism (hirsutism is the pathologic growth of hair in androgen-dependent regions); a thin fragile skin with wide purple striae on the abdomen, axillae, and thighs; proximal myopathy; and high blood pressure – 150/100 mm Hg (■ Figs. 3.1 and 3.2).

The initial laboratory tests showed dyslipidemia and impaired fasting glucose.

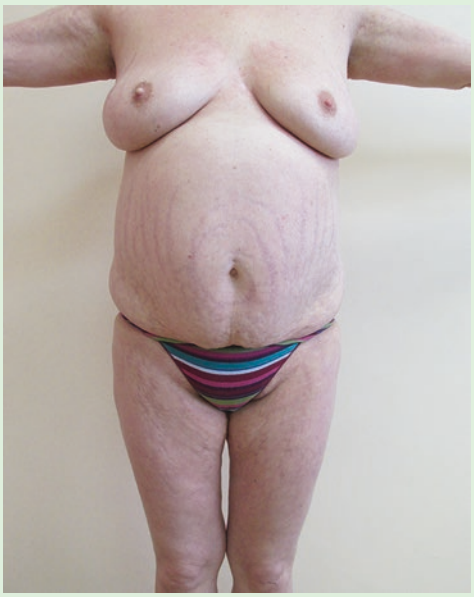

Fig. 3.1 General appearance of the patient revealing centripetal obesity; wide purple striae on the abdomen, axillae, and thighs; and proximal myopathy

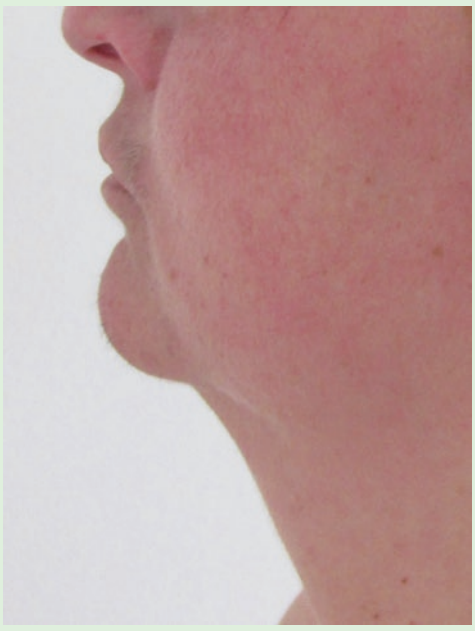

Fig. 3.2 Facial hirsutism in our patient

Considering the history of the patient and the findings from the physical and laboratory examination, is there any clinical suspicion of hypercortisolism? Does the patient have any signs and symptoms specific for CS?

Among the subject groups, which the Endocrine Society guideline recommends to be tested for CS, are the patients with (1) multiple and progressive features, particularly those with a high discriminatory value for hypercortisolism, and (2) unusual features for age.

Hypercortisolism is a syndrome of diverse clinical features. Most of them, however, are quite common in the general population (weight gain, acne, hirsutism, menstrual abnormalities, osteoporosis), and very few, if any, are specific for CS, e.g., catabolic features (proximal myopathy, purple striae, easy bruising) and centripetal obesity.

In addition to the alarming signs compatible with the syndrome (centripetal obesity, wide purple striae, easy bruising, proximal myopathy), our patient presented with arterial hypertension at a much earlier age than would otherwise be expected. Indeed, early onset of hypertension (i.e., <30 years) should raise suspicion of secondary hypertension (endocrine hypertension in our case). Her bone mineral density was normal.

Given the high prevalence of many of the signs and symptoms of hypercortisolism in the general population and the rarity of CS, there is a certain risk for false-positive diagnosis. Therefore, careful consideration should be given to identification of the patients with substantial clinical suspicion of hypercortisolism who are eligible for further biochemical testing. (The symptoms of CS are presented in detail in the chapter on adrenal Cushing's syndrome (► Chap. 27).)

What are the first-line biochemical tests to be done in a patient with suspected hypercortisolism?

Before conducting any laboratory tests for establishing the presence of hypercortisolism, the possibility of iatrogenic CS due to exogenous glucocorticoid exposure must be excluded.

The following measurements are recommended for initial testing:

1. Urinary free cortisol (UFC)
2. Late-night cortisol (salivary or serum)
3. 1 mg overnight dexamethasone suppression test (DST) with administration of dexamethasone between 23:00 h and midnight and measurement of serum cortisol between 08:00 and 09:00 h on the next morning

The screening tests reflect different physiologic abnormalities in CS: excessive integrated daily cortisol production (UFC), loss of diurnal cortisol nadir (late-night cortisol), and impaired response to glucocorticoid negative feedback (DST). Thus, they are complementary, and the use of more than one test is particularly helpful, especially considering that each one of them has its limitations.

Diagnostic criteria that suggest CS are:

- UFC greater than the normal range for the assay
- Late-night salivary cortisol above the normal range
- "Awake" late-night serum cortisol level of >7.5 μg/dL (207 nmol/L)
- Serum cortisol >1.8 μg/dl (50 nmol/L) after 1 mg overnight DST

As our patient had no past history of steroid drug use, we proceeded to biochemical confirmation of CS – the first diagnostic step.

The initial laboratory tests showed:

- UFC: 450.4 nmol/24 h [normal range, 38–275 nmol/24 h]
- Late-night serum cortisol: 1291.9 nmol/L
- Serum cortisol after 1 mg overnight DST: 276.2 nmol/L

Thus, the clinical suspicion of hypercortisolism was confirmed biochemically.

Is there a possibility of a functional hypercortisolic state, i.e., pseudo-Cushing in this patient?

The terms "functional hypercortisolic state," "hypercortisolism in the absence of Cushing's syndrome," and "pseudo-Cushing" refer to conditions associated with unspecific overactivity of the hypothalamic–pituitary–adrenal (HPA) axis. This could be observed during pregnancy and intense chronic exercise or in patients suffering from major psychiatric disorders, chronic alcoholism, poorly controlled diabetes mellitus, morbid obesity, malnutrition, and anorexia nervosa. In these conditions, higher brain centers stimulate corticotropin-releasing hormone (CRH) release with subsequent activation of the entire HPA axis, but without true CS, i.e., hypercortisolism is not autonomous. Nevertheless, it may produce results of the screening tests suggestive of CS (usually mild). Therefore, the 2 mg 48 h (low-dose) DST (4 × 0.5 mg dexamethasone for 2 days) is recommended as an optimal test for distinguishing between CS and pseudo-Cushing. The 2 mg 48 h low-dose DST can be combined with a CRH test (see later) at the end (Janovsky test).

Our patient did not present with any of the conditions associated with pseudo-Cushing – it was considered unlikely, and we proceeded to establishing the cause of the CS.

What is the cyclical Cushing's syndrome?

Cyclical CS is a rare condition where periods with active CS and eucortisolemia alternate. It can occur in all forms of endogenous CS, but most often in

CD. Hormonal tests will only be positive for CS during the active periods.

What is the first step in identifying the source of hypercortisolism?

After the diagnosis of CS is established, ACTH is measured as a first step to determine its cause. In the patients with low or undetectable values, ACTH-independent CS is suspected, and they should next undergo adrenal gland imaging. Those with normal (but inappropriate relative to the increased cortisol levels) or elevated ACTH values should undergo additional testing required for the differential diagnosis of ACTH-dependent CS (CD or ectopic CS). Usually, the higher the ACTH concentrations are, the more likely an ectopic source is considered. There are, however, no cutoffs proven to differentiate unequivocally CD from ectopic CS, as well as ACTH-dependent from ACTH-independent CS (up to 40% of the patients with ACTH-independent CS might have ACTH values in the normal range).

The serum ACTH level of our patient was 20.7 pmol/L [normal range, 2.2–12.2 pmol/L] – a concentration consistent with ACTH-dependent CS. The nearly twofold elevation of ACTH requires further comprehensive testing to distinguish CD from ectopic CS.

Given the limitations of ACTH measurement, could pituitary MRI be conclusive in the differential diagnosis between different forms of CS?

The large majority (90%) of the pituitary adenomas causing CD are microadenomas and are detectable on MRI in only ~60% of the patients. It is suggested that 40–60% of the patients with CD have occult corticotroph microadenomas that are not visible even on pituitary MRIs performed at experienced centers. On the other hand, 10% of healthy adults have pituitary lesions on MRI. Small pituitary adenomas can be observed in patients with ectopic CS as well. Hence, the presence of a lesion does not definitively confirm the diagnosis of CD or identify the causal tumor. However, the detection of a pituitary lesion compatible with an adenoma, especially if at least 5–6 mm in diameter, is suggestive of CD.

The MRI of our patient showed a 5.5 mm intrasellar adenoma. Nevertheless, we continued our investigations to exclude the possibility (even if not high) of ectopic CS.

What other tests could be useful in the differential diagnosis between CD and ectopic CS?

The differentiation between CD and ectopic ACTH secretion could be quite difficult, but is essential for appropriate therapy. Algorithms are based on imaging studies, biochemical tests, such as the CRH stimulation test, high-dose dexamethasone suppression test (HDDST), as well as the bilateral inferior petrosal sinus sampling (BIPSS) when the abovementioned imaging and biochemical investigations prove inconclusive.

The HDDST relies on the principle that ACTH secretion in CD usually undergoes partial or full suppression by high doses of dexamethasone, whereas ectopic tumors exhibit no sensitivity to glucocorticoids. HDDST can be performed either in a 2-day protocol (4 × 2 mg dexamethasone daily (altogether 16 mg for 2 days) or in an overnight manner (8 mg dexamethasone taken at midnight and blood drawn the next morning). Various thresholds have been proposed, with a percentage of urinary or serum cortisol suppression varying from 50% to 90%, or a serum cortisol concentration <50 nmol/L (or <140 nmol/L) on day 3.

In our patient a borderline response to the HDDST was observed. This justified further investigation, and therefore a CRH stimulation test was performed.

The diagnostic utility of the CRH test (similar to the HDDST) is also based on the rationale that corticotropinomas, but not ectopic ACTH-secreting tumors, usually retain some responsiveness to normal

regulatory mechanisms. The administration of CRH results in the increase of ACTH and cortisol levels due to the expression of CRH receptors by the adenomatous corticotroph cells, and the more intense the response is, the more likely the diagnosis of CD is. However, there isn't any definitive cutoff value to distinguish between CD and ectopic ACTH secretion, either. Nevertheless, an increase in the serum ACTH and cortisol levels >50% within 30 minutes of CRH administration could suggest CD.

In our case, ACTH concentrations increased slightly more than twofold (from 13.1 pmol/L to 26.4 pmol/L), and serum cortisol showed an elevation of almost 50% – from 387.4 nmol/L to 566.4 nmol/L. The results are thus compatible with CD.

What kind of invasive test can be done to differentiate Cushing's disease and ectopic ACTH syndrome?

A reliable, but invasive, test that could allow for the discrimination between CD and ectopic CS is BIPSS. It compares ACTH levels in peripheral vessels and in both sides of the inferior petrosal sinus (IPS) after CRH administration. CD is suggested by IPS/peripheral ACTH ratios >2 prior to CRH stimulation and by ratios >3 after its administration. BIPSS is considered by some authors as the "gold standard" for distinguishing ectopic CS from CD. In current algorithms, BIPSS is proposed as a third-line test, after pituitary MRI and dynamic endocrine tests. The safety and efficacy of the procedure are adequate with trained neuroradiologists.
Unfortunately, the patient did not follow our recommendation and referred to an inexperienced center, where the catheterization was performed without CRH stimulation and the results could not be interpreted. In order to further exclude the possibility of ectopic CS, we performed some additional investigations – CT/MRI imaging of the thorax and abdomen, ^{18}FDG-PET-CT, serum 5-hydroxyindoleacetic acid, and chromogranin A (biochemical markers for neuroendocrine tumors). None of them showed pathological findings.

In conclusion, based on the serum ACTH levels, the MRI data for a pituitary microadenoma, the response of the serum ACTH and cortisol during the HDDST and the CRH stimulation tests, the normal serum potassium levels, the absence of any pathological findings from the other imaging studies, as well as the relatively slow progression of the symptoms (for at least 3 years), the diagnosis of CD was established in our patient.

What is the first-line treatment for CD?

At present, transsphenoidal surgery (TSS), performed by an experienced pituitary neurosurgeon, is the treatment of choice for the vast majority of patients with CD (exceptions being patients with contraindications to surgery or those who decline surgery). About 65–90% of the patients with microadenomas and 40–65% of those with macroadenomas achieve endocrine remission after TSS by an experienced surgeon.

Following the recommendations, we referred our patient to an experienced pituitary neurosurgeon who performed a TSS with gross total resection of the adenoma.

What are the criteria of remission and the predictors of recurrence after a TSS?

Shortly after a successful resection of an ACTH-producing tumor, both ACTH and cortisol concentrations are expected to be low because normal corticotroph cells are not able to overcome suppression by the preceding hypercortisolism in the early postoperative period. Remission is generally defined as morning serum cortisol values <5 μg/dL (138 nmol/L) or UFC < 10–20 μg/24 h (28–56 nmol/24 h) after selective tumor resection. Higher levels are usually a sign of unsuccessful surgery and require further testing. Major predictors of recurrence are also the evi-

dence of a macroadenoma preoperatively (45% vs. 20–30% in microadenomas) and early recovery of the HPA axis (within the first 6 months after the TSS).

Measurement of baseline morning cortisol and/or serum cortisol response to ACTH stimulation test or insulin-induced hypoglyce ia is recommended to assess the recovery of the HPA axis.

Recurrence is established by the tests used for the screening of hypercortisolism. The increased late-night cortisol appears to be the earliest biochemical sign of recurrence mainly due to residual tumor. In some cases, a CRH stimulation test might be useful, and an increase of ACTH and cortisol levels is indicative for a residual tumor.

In addition to biochemical tests, a postoperative pituitary MRI scan should be obtained within 3–6 months after the TSS.

Our patient was admitted for postoperative evaluation 3 months after the TSS. She claimed that she was feeling better after the surgery and had lost some weight. The laboratory tests revealed, however, that she was still hypercortisolemic – her UFC was 561.1 nmol/24 h [normal range, 38–275 nmol/24 h], and her late-night serum cortisol was 934.9 nmol/L. There was no improvement in her blood pressure, lipid profile, and carbohydrate metabolism, either. The postoperative MRI scans showed no residual adenoma.

What are the second-line treatment options after an unsuccessful TSS?

In the patients with CD who underwent a non-curative surgery, there are several available second-line therapies including repeat TSS, radiotherapy, medical therapy, and bilateral adrenalectomy. Patients with persistent or recurrent CD after initial TSS may undergo a second surgical procedure. Of note, endocrine remission is far less likely after repeat TSS, and the risk of surgical complications appears to be higher. Moreover, repeat TSS is recommended in patients with evidence of incomplete resection, or a pituitary lesion on imaging.

Therefore, this did not appear to be a reasonable option in our case.

Radiation-based therapies can also be considered if CD is sustained after surgery. They include fractionated radiotherapy and stereotactic radiotherapies (Gamma Knife surgery, CyberKnife, and proton beam therapy). They have, however, significant limitations:

- The effect only begins to manifest itself after an average of 2 years.
- Tumor control is observed in 83–100% of patients, but endocrine remission occurs in 28–84% after a variable time interval during which patients require medical therapy to control hypercortisolism.
- Hypopituitarism is observed in approximately 40% of the patients (up to 85% after 15 years).
- Might be accompanied by secondary brain tumors in 1–2% of the patients.
- There is a risk of optic neuropathy (1–2%) and other cranial neuropathies (1%).
- The risk of stroke is increased.

Based on the evidence that tumor size is better controlled than hypercortisolism, radiotherapy is recommended predominantly in the cases raising concerns about mass effects or invasion associated with corticotroph adenomas.

Given that our patient had no visible residual lesion on the postoperative MRI scans, we refrained from radiotherapy and opted for the other remaining treatment of choice – medical therapy. The medications most frequently used for the treatment of CS are inhibitors of adrenal steroidogenesis. In the cases of Cushing's disease, another medical treatment option is pituitary-directed therapy as well as glucocorticoid receptor antagonists (e.g., mifepristone). Tumor-targeted pharmacological treatment (dopamine agonist cabergoline and second-

generation somatostatin analog pasireotide) leads to normalization of UFC in 20–40% of the patients.

In our patient, the steroidogenesis inhibitor ketoconazole was initiated. Ketoconazole administration (600 mg/d) resulted in UFC and late-night serum cortisol normalization. The patient continued to lose some weight, her blood pressure improved, and a couple of months later, her menstrual cycle became regular again.

What are the main concerns associated with Ketoconazole therapy?

Adverse effects associated with ketoconazole include:

- Disturbances of the digestive system
- Inhibition of testosterone biosynthesis resulting in hypogonadism and gynecomastia in men; interference with the masculinization of a male fetus (female patients should avoid pregnancy)
- Hepatotoxicity
- Substantial potential for drug–drug interactions with agents metabolized by the cytochrome P4503A4 system
- QT prolongation

Fortunately, our patient had no major side effects, except for some gastrointestinal discomfort and mild asymptomatic elevation of transaminases.

What are the pros and cons of bilateral adrenalectomy (BA) in patients with CD?

Case Continued

A year and a half after initiation of the treatment, however, an escape phenomenon was observed: elevated late-night and urinary free cortisol. As the patient did not tolerate higher doses of ketoconazole, it was discontinued and substituted with pasireotide (2 × 0.6 mg/d), which had meanwhile become commercially available.

Pasireotide is a multi-ligand somatostatin analog able to bind somatostatin receptors 1, 2, 3, and 5, which became the first approved tumor-targeted pharmacological treatment of CD. It is shown to normalize UFC, decrease tumor volume, and improve some of the clinical signs of hypercortisolism.

Under the treatment with pasireotide, our patient showed progression of the initially established impaired fasting glucose to overt diabetes. Moreover, she turned out to be a complete nonresponder to pasireotide, and a couple of months later, it was discontinued.

Afterward, she was enrolled in a clinical trial with a novel inhibitor of adrenal steroidogenesis. During the next almost 2 years, her condition improved significantly – both serum and urine cortisol levels normalized; body weight decreased, as well as facial hair growth and blood pressure; and menstruation became regular again. Unfortunately, 2 years after enrollment in the study, loss of response was observed. MRI scans still showed no pituitary lesion.

After extensive discussions we decided to exploit our last treatment option – bilateral adrenalectomy.

BA provides rapid and definitive control of hypercortisolism and may be considered for the patients who have recurrent CD, for whom surgical, medical, and radiation-based therapies have failed or are not appropriate, or for those who are intolerant of the side effects of these treatment modalities. BA may also be elected upon by the patients who are concerned about the potential adverse events associated with radiotherapy as well as by women who are planning to conceive. It is almost always performed laparoscopically with low morbidity and a 10-year mortality of 3% in patients with CD.

However, BA leads to permanent

primary adrenal insufficiency and the consequent requirement for lifelong glucocorticoid and mineralocorticoid replacement. In addition, it has been associated with subsequent corticotroph tumor progression (in about 50% of the patients), which may further progress to Nelson syndrome (in 8–20%) due to the falling out of the negative feedback after BA (pituitary ACTH-producing tumors retain some responsiveness to cortisol feedback as shown in the dynamic test with high-dose dexamethasone). In these cases, tumor growth may cause mass effect and significant elevation in ACTH levels, leading to skin hyperpigmentation. Nelson syndrome is less likely in the patients without visible tumor at the time of adrenalectomy (as in our case) or in those who had pituitary radiotherapy.

What evaluations are recommended in our patient after the BA?

Postoperatively glucocorticoid and mineralocorticoid replacement was initiated – prednisone (5 + 2.5 mg/d) and fludrocortisone acetate (50 μg/d). Up to date the patient is adequately substituted and has no complaints. Long-term follow-up is underway.

Apart from careful control of the replacement therapy, lifelong follow-up is mandatory because of the possibility of Nelson syndrome. Although the likelihood is very low considering that the last MRI scans showed no pituitary lesion, regular investigations should include clinical examinations for hyperpigmentation, ACTH measurements, and MRI scans evaluating for corticotroph tumor progression.

What other considerations should be kept in mind?

The signs and symptoms of CS resolve gradually over a period of 2–12 months after effective cure. Long-term follow-up should include also monitoring and adjunctive treatment for the specific comorbidities associated with CS (e.g., cardiovascular risk factors, osteoporosis, psychiatric disorders, increased risk for thromboembolism) until their resolution. Some patients may also have impaired quality of life despite the remission of hypercortisolism, and there are findings showing permanent neurological–psychiatric alterations in the patients already free of disease.

It should be noted that 5 years after remission, cardiovascular risk is higher in CD patients than in general population and the extent of recovery from these complications is inversely associated with the duration of hypercortisolism. Despite available treatments for comorbidities, mortality of the patients with CD is still higher than that of the general population.

Tips

The reader is advised to read the two other chapters on hypercortisolism: adrenal Cushing's syndrome (▶ Chap. 27) and ectopic ACTH syndrome caused by a bronchial neuroendocrine tumor (▶ Chap. 45). The symptoms of Cushing's syndrome are presented in more detail in the chapter on adrenal Cushing's syndrome.

Take-Home Messages

- Cushing's disease (CD) is caused by pituitary ACTH-secreting tumors and is the most common form of endogenous Cushing's syndrome.
- Prolonged hypercortisolism leads to significant comorbidities, increased mortality, and impaired quality of life in patients with CD.
- The early accurate diagnosis and treatment of CD has an impact on long-term outcomes.
- Optimal treatment involves localization and complete resection of the ACTH-secreting pituitary adenoma.
- In patients with CD not cured by pituitary surgery, medical therapy targeting the corticotroph tumor such as cabergoline and pasireotide is a second-line option.
- Inhibitors of adrenal steroidogenesis could be used to control hypercortisolism in some patients if corticotroph-targeting therapy is not effective.
- Pituitary irradiation is another second-line treatment for persistent or recurrent CD.
- Bilateral adrenalectomy is a definitive treatment for ACTH-secreting pituitary tumors.
- Patients may have impaired quality of life for many years despite the remission of hypercortisolism.

Suggested Reading

1. Aranda G, Enseñat J, Mora M, Puig-Domingo M, Martínez de Osaba MJ, Casals G, Verger E, Ribalta MT, Hanzu FA, Halperin I. Long-term remission and recurrence rate in a cohort of Cushing's disease: the need for long-term follow-up. Pituitary. 2015;18(1):142–9. https://doi.org/10.1007/s11102-014-0567-8.
2. Castinetti F, Brue T, Ragnarsson O. Radiotherapy as a tool for the treatment of Cushing's disease. Eur J Endocrinol. 2019;180:D9–D18. https://doi.org/10.1530/EJE-19-0092.
3. Cuevas-Ramos D, Fleseriu M. Medical treatment of Cushing's disease. Minerva Endocrinol. 2016;41(3):324–40. Epub 2016 Mar 15
4. Fleseriu M, Hamrahian AH, Hoffman AR, Kelly DF, Katznelson L, AACE Neuroendocrine and Pituitary Scientific Committee. American Association of Clinical Endocrinologists and American College of Endocrinology Disease State clinical review: diagnosis of recurrence in cushing disease. Endocr Pract. 2016;22(12):1436–48. https://doi.org/10.4158/EP161512.DSCR.
5. Nieman LK. Recent updates on the diagnosis and management of Cushing's syndrome. Endocrinol Metab. 2018;33(2):139–46. https://doi.org/10.3803/EnM.2018.33.2.139.
6. Nieman LK, Biller BMK, Findling JW, Newell-Price J, Savage MO, Stewart PM, Montori VM. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metabol. 2008;93(5):1526–40. https://doi.org/10.1210/jc.2008-0125.
7. Nieman LK, Biller BMK, Findling JW, Murad MH, Newell-Price J, Savage MO, Tabarin A, Endocrine Society. Treatment of Cushing's syndrome: an endocrine society clinical practice guideline. J Clin Endocrinol Metabol. 2015;100(8):2807–31. https://doi.org/10.1210/jc.2015-1818.
8. Pivonello R, De Leo M, Cozzolino A, Colao A. The treatment of Cushing's disease. Endocr Rev. 2015;36(4):385–486. https://doi.org/10.1210/er.2013-1048.
9. Pivonello R, Isidori AM, De Martino MC, Newell-Price J, Biller BMK, Colao A. Complications of Cushing's syndrome: state of the art. Lancet Diabetes Endocrinol. 2016;4(7):611–29. https://doi.org/10.1016/S2213-8587(16)00086-3.
10. Rubinstein G, Osswald A, Zopp S, Ritzel K, Theodoropoulou M, Beuschlein F, Reincke M. Therapeutic options after surgical failure in Cushing's disease: a critical review. Best Pract Res Clin Endocrinol Metab. 2019;19:1187–200. https://doi.org/10.1016/j.beem.2019.04.004.
11. Theodoropoulou M, Reincke M. Tumor-directed therapeutic targets in Cushing disease. J Clin Endocrinol Metabol. 2019;104:925–33. https://doi.org/10.1210/jc.2018-02080.
12. Tritos NA, Biller BMK. Current management of Cushing's disease. J Intern Med. 2019;286(5):526–41. https://doi.org/10.1111/joim.12975.
13. Wong A, Eloy JA, Liu JK. The role of bilateral adrenalectomy in the treatment of refractory Cushing's disease. Neurosurg Focus. 2015;38(2):E9. https://doi.org/10.3171/2014.10.FOCUS14684.
14. Yamada S, Inoshita N, Fukuhara N, Yamaguchi-Okada M, Nishioka H, Takeshita A, Suzuki H, Ito J, Takeuchi Y. Therapeutic outcomes in patients undergoing surgery after diagnosis of Cushing's disease: a single center study. Endocr J. 2015;62(12):1115–25. https://doi.org/10.1507/endocrj.15-0463.
15. Young J, Haissaguerre M, Viera-Pinto O, Chabre O, Baudin E, Tabarin A. Management of endocrine disease: Cushing's syndrome due to ectopic ACTH secretion: an expert operational opinion. Eur J Endocrinol. 2020;182(4):R29–58. https://doi.org/10.1530/EJE-19-0877.

Non-functioning Pituitary Adenoma

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Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_4

Opening

This chapter discusses the group of non-functioning pituitary adenomas, their symptoms, laboratory and imaging features, and treatment issues.

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Definition of the Disease

Pituitary adenomas are benign, epithelial neoplasms that originate from the adenohypophyseal cells and represent 10–15% of all intracranial tumors. According to their size, they are classified into microadenomas (<10 mm), macroadenomas (>10 mm), and giant adenomas (>40 mm). About two-thirds of pituitary adenomas cause hormone hypersecretion with corresponding clinical symptoms of prolactinoma (► Chap. 1), acromegaly (► Chap. 2), or Cushing's disease (► Chap. 3), respectively. TSH-secreting tumors leading to secondary hyperthyroidism are casuistic (incidence is approximately 1–2/million/year). Clinically non-functioning pituitary adenomas (NFPAs) comprise approximately 22–54% of all pituitary adenomas. Their prevalence is 7–41 cases/100,000 with a bimodal peak incidence (ages of 25–45 and 60–70 years). The annual incidence is estimated to be 0.65–2.34 cases/100,000, and there is no gender predominance. NFPAs are a heterogeneous group of usually slowly growing tumors with different histological subtypes. According to the classification of endocrine tumors of the World Health Organization (WHO 2017), based on the immunohistochemical expression of pituitary hormones and pituitary-specific transcriptional factors, NFPAs are classified into eight subtypes: silent gonadotroph, corticotroph, somatotroph, thyrotroph, lactotroph, plurihormonal Pit-1, null cell, and double/triple NFPA. Silent gonadotropinomas are the most common type, and in spite of the positive expression of LH, FSH, or their subunits, the serum concentrations of the corresponding hormones are usually within normal range and are not associated with typical clinical features. "Null cell adenomas" are exclusively rare pituitary neoplasms characterized by immunonegativity for all adenohypophyseal hormones and a lack of cell-type specific transcription factors.

Case Presentation

We present a case of a 52-year-old man, who manifested severe headaches and progressive loss of vision at the age of 30. The patient had no other complaints. Except for visual disturbance, physical examination revealed no other abnormality. Computed perimetry demonstrated visual field defects, more pronounced in the left eye. Magnetic resonance imaging (MRI) visualized a pituitary macroadenoma 30 × 39 × 31 mm in size, with para- and suprasellar expansion.

What are the features from this case that are suspicious for NFPA?

Combination of severe headaches, visual disturbances, and lack of specific symptoms related to hypersecretion of adenohypophyseal hormones in our case is a strong argument in favor of non-functioning pituitary macroadenoma.

NFPA is a heterogeneous group that varies from completely asymptomatic to clinically manifested tumors. Most of them are incidentally diagnosed on MRI or CT as asymptomatic microadenomas

(pituitary incidentalomas). In non-functioning macroadenomas, the main symptoms resulting from the mass effect of the tumor are headache, visual disturbances, ophthalmoplegia, pituitary apoplexy, and pituitary hormone deficiency. Headache and visual field abnormalities, which are the major manifestations in our clinical case, are among the most common complaints occurring in 60–80% of all patients. Tumor enlargement stretches the sellar diaphragm with subsequent activation of the pain receptors of the dura mater. Patients complain about headaches mostly in the frontal and occipital regions. Although visual field defects (quadrantanopia, bitemporal hemianopsia) are common, the prevalence of ocular motor abnormalities due to involvement of cranial nerves III, IV, and VI is very low (less than 5%).

Case Presentation Continued

After surgery, there was clinical improvement and residual tumor with significantly reduced volume on the early postoperative MRI. The patient had no complaints and was lost to follow-up for more than 2 years.

What mistakes were made in the out-patient preoperative management of the patient?

The main questions to be answered in the preoperative assessment of every patient diagnosed with pituitary adenoma apart from tumor size are:

1. *Is there pituitary hormone oversecretion?* - Preoperative hormonal assessment should include laboratory tests for hyperprolactinemia, hypercortisolism, and growth hormone oversecretion. It enables distinguishing hormone-secreting adenomas from NFPA and identifies potential candidates for conservative treatment (dopamine agonist therapy in patients with prolactinomas). It also provides reliable biomarkers for postoperative follow-up of subjects with hormone-secreting adenomas.
2. *Is there pituitary hormone deficiency?* - Screening for secondary hypogonadism, hypothyroidism, and adrenal insufficiency (but not hyposomatotropism) is recommended at diagnosis of all cases with pituitary macroadenomas (with or without clinical symptoms) (► Chap. 6 on hypopituitarism). Patients with confirmed pituitary deficiencies require preoperative hormone replacement therapy with glucocorticoids and levothyroxine in order to reduce the risk for perioperative hypopituitarism- and anesthesia-related complications.
3. *Is the imaging technique reliable enough?* - Contrast-enhanced MRI is the preferred method for the imaging of pituitary adenomas, which enables most accurate visualization of the tumor expansion to important neighboring anatomical structures such as cavernous sinus and optic chiasm. CT should be performed only in patients contraindicated for MRI.

The lack of preoperative hormonal assessment in the presented case of a large macroadenoma not only leads to incomplete diagnosis but also determines increased intraoperative risk for the patient if there is hypopituitarism.

Which laboratory tests are recommended in patients with newly diagnosed apparently NFPA?

Before laboratory testing, physicians have to take detailed patient's history and perform a full physical examination with targeted search for the classical signs and symptoms of hypopituitarism or hormone hypersecretion of PRL (oligoamenorrhea; galactorrhea in women, impaired libido, and gynecomastia in men), GH (typical signs of acromegaly), ACTH (overt or subclinical Cushing's syndrome), or TSH (secondary hyperthyroidism). Laboratory tests should include basal measurements

of prolactin (PRL), thyrotropin (TSH), free thyroxine (FT4), adrenocorticotropic hormone (ACTH), cortisol, LH, FSH, estradiol (in women), testosterone (in men), growth hormone (GH), insulin-like growth factor 1 (IGF-1), and alpha subunit of glycoproteins (if possible).

A predominant part of NFPA produce *gonadotropins*, but most of them are not able to secrete them into circulation, so elevated baseline subunits of FSH and/or LH are found in 30% of cases. It is important to note that α-subunit may be the sole biochemical marker of the gonadotroph subtype NFPA in most patients.

Regarding *corticotropinomas*, there is a wide spectrum of ACTH secretion between "silent" and secreting forms. Progression from clinically silent corticotroph adenomas toward overt hypercortisolism is rare. Screening for cortisol excess should include urinary free cortisol, ACTH, and overnight 1 mg dexamethasone test.

Exploration for *hypopituitarism* should be performed with assays of all anterior pituitary hormones and the corresponding peripheral hormones. If this is not possible, the minimum test panel should include morning basal levels of FT4, cortisol, LH, FSH, E2 (in women) and testosterone (in men). (see chapter on hypopituitarism (▶ Chap. 6).

The most frequent deficit is central (secondary/hypogonadotropic) hypogonadism, followed by secondary hypothyroidism and secondary adrenal insufficiency. No laboratory testing for hypogonadism is required in women with spontaneously regular menstrual cycle. In young women with amenorrhea, serum FSH value should be interpreted very carefully. In postmenopausal women who are not on hormone replacement therapy, the absence of physiological elevation of FSH and LH is consistent with secondary hypogonadism. In men, central hypogonadism presents with low serum testosterone, low or inappropriately normal gonadotropins, and features of testosterone deficiency. Secondary hypothyroidism should be suspected if fT4 levels are decreased in combination with low or normal TSH. Secondary adrenal insufficiency manifests itself with low baseline serum cortisol at 8 a.m. and blunted cortisol response to corticotropin/insulin stimulation tests. GH deficiency occurs in more than half of patients with hypopituitarism and is confirmed by IGF-1 concentrations lower than the gender- and age-specific normal range.

According to the patient's history, he never experienced clinical signs suspicious for any pituitary hormone oversecretion. As the patient was not referred to endocrinologist and hormonal tests were not performed, preoperative hypopituitarism in this case can neither be confirmed nor ruled out.

? Are dynamic tests recommended for diagnosis or follow-up in patients with NFPA?

- Overnight 1 mg dexamethasone (DXM) test is recommended as a screening test for cortisol excess.
- Stimulatory tests (short ACTH stimulation (cosyntropin) test or insulin hypoglycemia test) are recommended if secondary adrenal insufficiency is suspected.
- GnRH or TRH stimulation tests are not recommended for diagnosis or follow-up of NFPA, being not reliable enough and predisposing although rarely to a serious risk for pituitary apoplexy.

? What are the typical MRI characteristics of NFPA?

✓ *MRI* of the sellar region (preferably with gadolinium contrast) is the gold standard to evaluate NFPA. Thin (≤3 mm) sagittal and coronal T1- and T2-weighted slices and 3D volume assessment with reconstruction are strongly recommended. MRI is the preferred method for visualizing the relationship of NFPA with the optic chiasm, carotid arteries, and the degree of invasion into the cavernous sinuses and other surrounding structures.

- In *T1-weighted images,* the adenomas appear hypo- or isointense with delayed enhancement after contrast administration compared to normal pituitary. In patients with pituitary apoplexy, the hemorrhage appears as a hyperintense lesion in T1-weighted images without contrast.
- In *T2-weighted images*, the adenomas are isointense compared to the white matter.

Tumor dimensions (30 × 39 × 31 mm) and suprasellar adenoma expansion in our clinical case are strong negative predictors for surgical outcome.

What kind of growth patterns of a sellar mass can occur?

If the macroadenoma grows upward from the sellar cavity, it is termed suprasellar. Growth toward the sides is called parasellar, whereas downward it is infrasellar. These growth patterns can be combined, e.g., supra- and parasellar.

What could be the differential diagnosis in case of sellar mass with parasellar extension?

The differential diagnosis of NFPA is often challenging because of the similar MRI findings and clinical features of adenomas and other pituitary lesions. In cases with atypical radiological findings, other pathologies should be excluded such as non-pituitary tumors (craniopharyngiomas, germinomas, chordomas of the clivus, metastases), granulomatous disease (tuberculosis, syphilis, sarcoidosis), histiocytosis X, lymphocytic hypophysitis, pituitary hyperplasia, vascular aneurysms, etc.

Contrast-enhanced MRI imaging in our clinical case presented the typical hypointense compared to normal adenohypophysis pituitary mass with heterogeneous post-contrast enhancement on T1 images consistent with pituitary macroadenoma with extrasellar expansion and without MRI signs of apoplexy.

When is ophthalmologic assessment indicated?

Ophthalmologic assessment is not required in patients with microadenomas or macroadenomas that are far from the optic chiasm. In patients with visual complaints and in all cases of tumors adjacent to the optic chiasm or optic tracts on MRI, neuro-ophthalmologic assessment should comprise:

- Visual acuity assessment
- Visual field examination (computed perimetry; Goldmann method)
- Anterior segment examination
- Fundoscopy
- Oculomotor evaluation (to exclude diplopia)

Strict ophthalmologic surveillance should be performed in all patients in whom conservative management has been preferred. Treatment approach depends on the severity of visual defects and/or their progression during the follow-up.

- *NFPA close to or in contact with the optic* chiasm: If decision for conservative treatment is made, MRI, hormonal evaluation, and neuro-ophthalmologic assessment should be performed every 6 months. Thereafter, in cases with favorable evolution during follow-up, these procedures could be performed annually and then less frequently.
- *NFPA remote from the optic chiasm*: Without tumor progression at 1st year, further MRI surveillance can be performed every 2 years. Annual anterior pituitary hormonal evaluation is recommended.

What should be the first-line treatment of NFPA?

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The main treatment options for NFPA include active surveillance, surgical treatment, and radiotherapy. The treatment approach should be individualized, based on tumor size and behavior, pituitary function, patient's age and general condition, as well as the patient's preference. Most of NFPAs have a slow growth rate, approximately 0.6 mm/year according to literature data.

- *Watch-and-wait approach with regular surveillance* of tumor size and pituitary function is recommended for non-functioning microadenomas and macroadenomas remote from the optic chiasm.
- *Surgical approach* is indicated if tumor growth, visual field defects, pituitary dysfunction, or severe headaches are registered during follow-up. Urgent surgery is indicated in patients with pituitary apoplexy who develop neuro-ophthalmologic complications. Young patients, especially women planning pregnancy, are good candidates for surgery because of the higher risk for significant tumor enlargement. On the contrary, in elderly patients with comorbidities, decision for surgery should be made after careful benefit-risk consideration. Transsphenoidal surgery, performed by an experienced pituitary neurosurgeon, is the preferred method. Transcranial surgery has limited indications – large or gigantic tumors extending into the median fossa and the cavernous sinuses. Complete surgical removal of a NFPA is achieved in approximately 65% and postoperative improvement of visual disturbances in 80–90% of cases.

  Recurrence rate is around 20–30%, and the most significant recurrence predictors are the presence of tumor extension into the cavernous sinus and/or residual adenoma after initial surgery.

Case Presentation Continued

After ophthalmology and neurology consultations, the patient was referred directly to the Department of Neurosurgery (without endocrinology consultation and preoperative hormonal assessment!) and underwent non-radical transsphenoidal adenomectomy (TSA) in April 2008.

Important: The perioperative management algorithm depends on anterior pituitary function at diagnosis!

- In patients with *secondary hypothyroidism and/or secondary adrenal insufficiency*, replacement therapy should be started or adjusted if already initiated to improve the patient's general condition before surgery and to reduce perioperative risk. The most commonly used scheme for patients with preoperatively proven corticotroph deficiency is 48 hours' supraphysiological therapy with hydrocortisone: 50 mg TID (three times daily) on the day of surgery (D0), followed by 25 mg TID on the first day (D1) and a single dose of 25 mg at 8 a.m. on the second postoperative day (D2). Some expert teams recommend higher doses: 100 mg hydrocortisone IV upon induction of anesthesia and then 100 mg IV TID on the first and 50 mg BID on the second postoperative day. Patients are usually dismissed from the hospital on 20 mg daily dose hydrocortisone or another glucocorticoid in equivalent dose.
- In patients with intact hypothalamus–pituitary–adrenal axis (HPA) at diagnosis and if complete adenoma removal is possible, perioperative glucocorticoid replacement is not obligatory although some experts recommend it in order to prevent intraoperative stress corticotroph deficiency.

What kind of complications can be expected postoperatively and how to manage them?

In a recent meta-analysis on NFPA patients, transsphenoidal surgery is associated with 1% mortality. Postoperative complications such as diabetes insipidus, rhinoliquorrhea, meningitis, vascular injury, or new-onset visual field defects occur in less than 5% of all cases, predominantly in patients with large adenomas. Pituitary function should be reassessed 1–3 months after surgery, and substitution therapy should be started in patients with proven hormonal deficiencies. In the early postoperative period (7–10 days after surgery), the focus should be on the adequate substitution of corticotroph deficiency and diabetes insipidus if they exist.

1. *Secondary adrenal insufficiency (SAI)* – if left undiagnosed and untreated, it can result in severe, in some cases even fatal adrenal crisis. The most reliable marker for postoperative SAI is the morning serum cortisol level measured during the first week after surgery. Cortisol level at 8 a.m. <100 nmol/L is a positive predictor, and >450 nmol/L is a negative predictor for the presence of SAI. Levels between 100 and 450 nmol/L require dynamic tests.

   The *insulin tolerance test (ITT)* is considered to be the gold standard for assessment the integrity of the whole HPA axis, but is contraindicated in the elderly and patients with serious comorbidities (epilepsy, ischemic heart disease, cerebrovascular disease). The *short ACTH (cosyntropin, tetracosactide, Synacthen™) test (250 µg IV)* is inferior to ITT in the early postoperative period. (see the chapter on hypopituitarism for more details (► Chap. 6).
2. *Transient diabetes insipidus (DI)* occurs within the first 24–48 hours after surgery in up to 30% of patients. It is thought to be caused by a temporary traumatic dysfunction of vasopressin-producing neurons. Treatment with desmopressin acetate 5–10 µg TID or BID (twice daily) s.c. on the first and second postoperative day is recommended, switching to oral substitution with 0.1–0.2 mg TID or BID if DI persists.
3. *Transient syndrome of inappropriate antidiuretic hormone secretion (SIADH)* may also be observed within the first postoperative week, as a result of uncontrolled release of ADH. In rare cases, SIADH can manifest itself with severe, life-threatening, acute hyponatremia.

How often should postoperative follow-up hormonal evaluation, imaging studies, and ophthalmologic assessment be performed?

The first *postoperative MRI* should be performed 3–6 months after surgery, and then annual assessment is recommended during the first 5 years. If no recurrences are detected, imaging studies may be carried out every 2 years for the next 5 years.

Postoperative *ophthalmologic assessment* should be performed 3 months after surgery, and then the frequency of follow-up checkups depends on the visual status and the distance of the tumor from the optic chiasm.

Hormonal evaluation for hypopituitarism should be considered 1–3 months after surgery and every 6–12 months thereafter. The risk of new-onset pituitary deficiency is about 10% per year.

What are the second-line treatment options after an unsuccessful neurosurgery?

Repeated surgery: According to literature, 30–48% of patients operated on for NFPA undergo surgical revision, although it does not seem to improve tumor control, with persistent residual disease in more than 70% of cases.

Medical therapy is usually not a successful strategy although most of NFPAs express dopaminergic (D2R), and about 80% of them have variable subtypes of somatostatin (mainly SSTR2 and SSTR3) receptors. On one side, NFPAs do not demonstrate good response to treatment. On the other hand, in contrast with functioning adenomas, the evaluation of the efficacy of medical therapy is limited by the lack of a measurable biochemical marker. The only indicator for therapeutic response in NFPA is the reduction in tumor volume on imaging studies. Therapeutic response to the dopamine agonist *cabergoline* up to 3 mg per week as postsurgical adjuvant treatment seems the most effective as 30–50% of treated patients show a significant reduction in residual tumor volume after 6–12 months of treatment. In one case-control study, the first-generation somatostatin analogue *octreotide LAR* demonstrated tumor remnant stabilization in 81% of patients with residual NFPA after a 3-year mean follow-up. There are several ongoing phase 2 randomized controlled trials with *pasireotide LAR* (a second-generation SST analogue acting on SSTR1, SSTR2, SSTR3, and STR5 subtypes) for the treatment of NFPA, but the initial results are not encouraging. *Temozolomide*, an alkylating chemotherapeutic drug, is used for control of aggressive pituitary tumors. Responsiveness to this drug is considered to be dependent on the immuno-expression of O-(6)-methylguanine DNA methyltransferase (MGMT), a DNA repair protein that acts by removing the alkyl group. Consequently, pituitary tumors with low MGMT expression demonstrate good response to temozolomide.

Radiotherapy as a primary therapy is only limited to the cases where surgery is contraindicated, or in inoperable cases. In general, radiotherapy is a postoperative treatment option for cases with large residual remnants and for NFPA showing progression after surgery. Stereotactic techniques (stereotactic radiosurgery or fractionated stereotactic radiotherapy) provide excellent tumor control in patients with NFPA (85–95% in 5–10-year follow-up) with more focused irradiation and lower risk for long-term side effects. Stereotactic RT may also be a good option for patients with aggressive highly proliferative tumors, with parasellar invasion. The major limitation of RT is the long-term risk of hypopituitarism, followed by the increased cerebrovascular morbidity and mortality.

Case Presentation Continued

After more than 2 years of clinical remission, at the end of 2010, our patient experienced relapse of his headaches and visual disturbances. MRI revealed significant residual tumor growth (50 × 31 × 32 mm) (Fig. 4.1) and panhypopituitarism was confirmed by hormonal analysis. Glucocorticoid and levothyroxine substitution was initiated, and transsphenoidal re-adenomectomy was performed in February 2011. The patient was referred to the University Clinic of Endocrinology (Expert Center for Pituitary Diseases) for the first time after the second transsphenoidal adenomectomy, with residual macroadenoma (43 × 30 × 34 mm) and hypopituitarism, on hydrocortisone and levothyroxine substitution therapy. Based on the full hormonal evaluation, uncontrolled panhypopituitarism was confirmed, and the doses of prednisone (7.5 mg/d) and levothyroxine (100 μg/d) were adjusted, and monthly long-acting testosterone intramuscular injections were started after contraindications were ruled out. Two more transsphenoidal surgeries (2011, 2013) were

carried out because of the aggressive behavior of the tumor. Immunohistochemistry revealed a null cell p53-positive pituitary tumor with MIB1/Ki-67 labeling index (LI) = 2%. The patient was in a stable good condition, with well-controlled hypopituitarism during the regular follow-up, but postoperative MRI still revealed a fast-growing aggressive tumor – residual pituitary mass 24 × 34 × 36 mm, adjacent to the optic chiasm (12 July 2013) (Fig. 4.2). After another routine discussion by a multidisciplinary team, the case was considered suitable for radiotherapy, and intensity-modulated radiotherapy (IMRT; dose of 54 Gy in 30 fractions) was performed in January–February 2015. Post-IMRT magnetic resonance imaging demonstrated significant reduction by 5–7 mm in all coronal and sagittal dimensions of the tumor on the second year and stable finding on the follow-up MRI scans (Fig. 4.3). There was a significant improvement of visual field defects (Figs. 4.4 and 4.5). The patient is completely asymptomatic, with well-controlled hypopituitarism under chronic substitution therapy with excellent compliance.

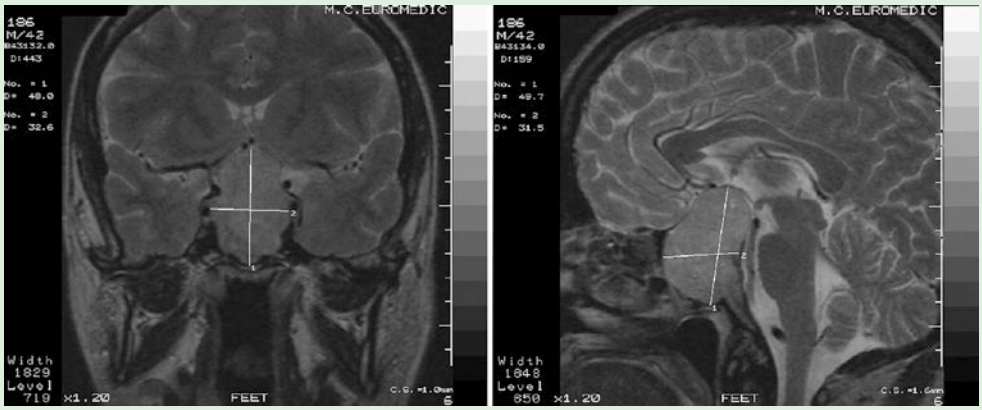

Fig. 4.1 MRI of the pituitary 3 years after the first TSA (transsphenoidal adenomectomy) (February 2011): coronal T1 (left panel) and sagittal T1 (right panel) post-contrast images

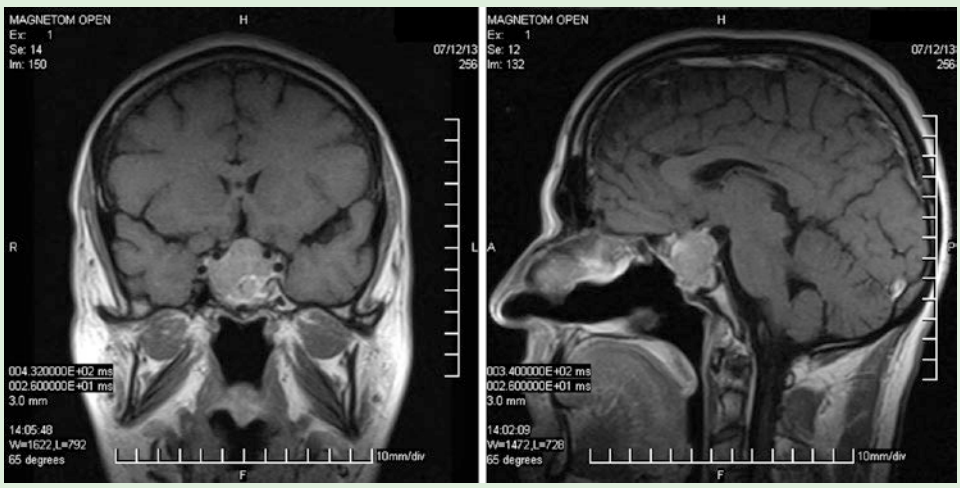

Fig. 4.2 MRI of the pituitary 3 months after the fourth TSA (July 2013): coronal T1 (left panel) and sagittal T1 (right panel) post-contrast images

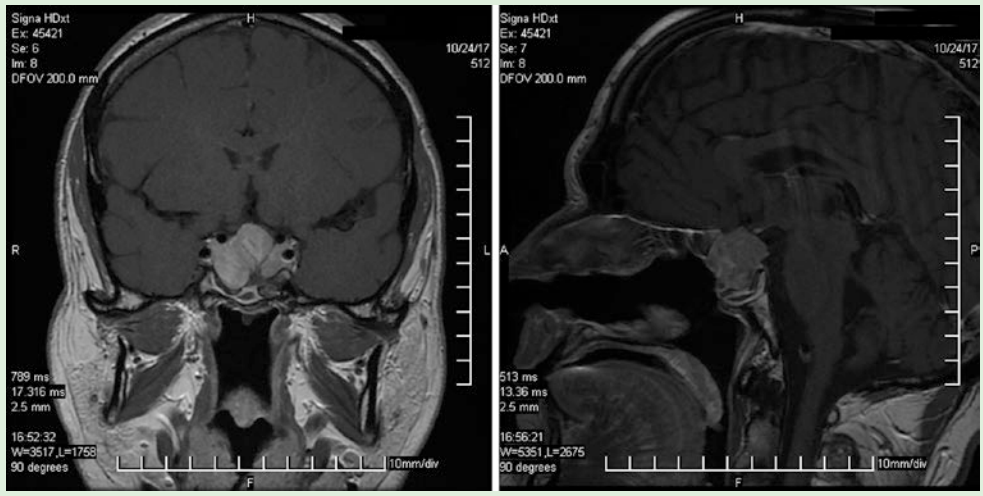

Fig. 4.3 MRI of the pituitary 32 months after the IMRT (intensity-modulated radiotherapy) (October 2017): coronal T1 (left panel) and sagittal T1 (right panel) post-contrast images

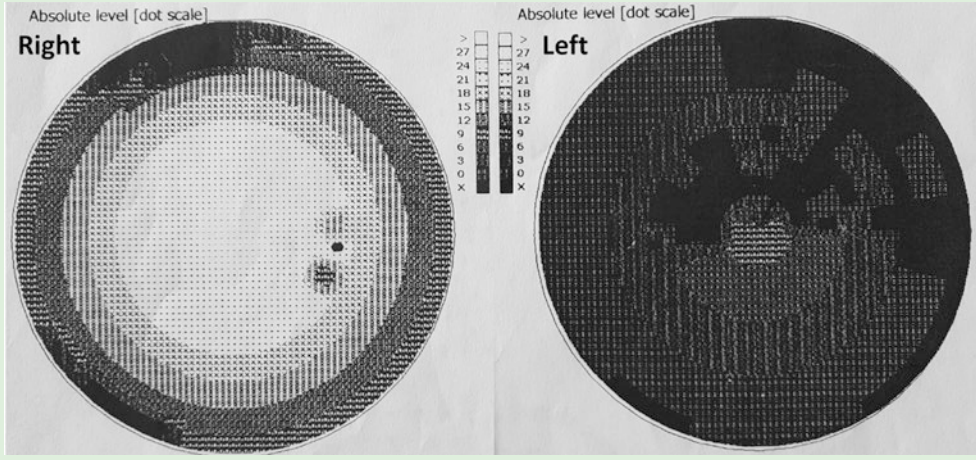

Fig. 4.4 Computed perimetry 1 month after the second TSA (March 2011)

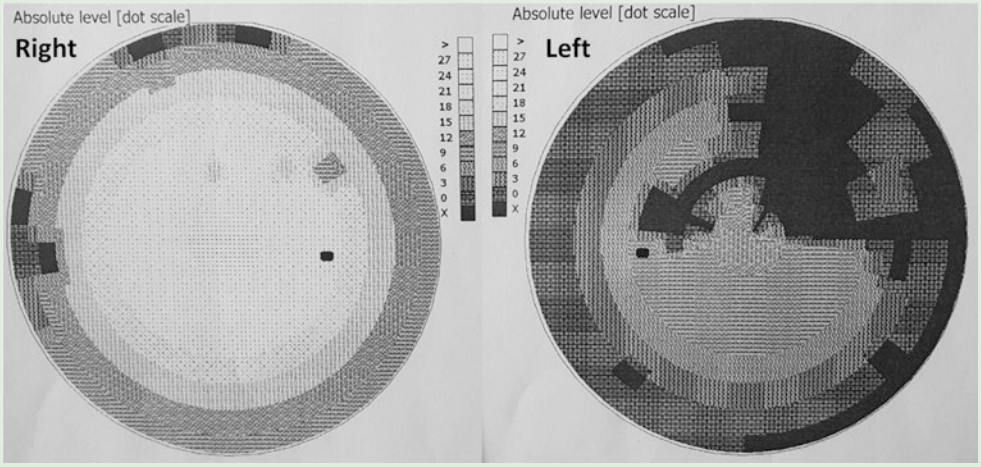

Fig. 4.5 Computed perimetry 5.5 years after the IMRT (June 2020)

Are there reliable prognostic factors in patients with NFPA?

Over the years, there has been an extensive search to identify reliable factors related to aggressiveness and the risk of recurrence in NFPAs. The presence of residual tumor, tumor growth rate (>80 mm^3/y), and suprasellar expansion are considered to be factors determining recurrence rate. Secondary progression is higher in conservatively followed patients (63%) compared to those who underwent surgery (36%), radiotherapy (13%), and combined surgery/adjuvant radiotherapy (13%). Other significant predictors for biologically aggressive tumor behavior are female gender, high IHC proliferative indexes (MIB1/Ki-67 > 3%; with 73% sensitivity and 97% specificity), and p53 positivity.

Case Presentation Conclusion

Despite the excellent response to radiotherapy and the proliferative index Ki-67 = 2%, which is lower than generally accepted cutoff (3%), p53 positivity of the above-presented NFPA requires close MRI surveillance. Cabergoline (high-dose) or temozolomide treatment could be discussed as adjunctive therapeutic option if tumor growth is observed through further follow-up.

Tips

The reader is advised to read the other chapters on pituitary adenomas including prolactinoma (▶ Chap. 1), acromegaly (▶ Chap. 2), and Cushing's disease

(▶ Chap. 3) and the chapter on hypopituitarism (▶ Chap. 6). Disorders of antidiuretic hormone (diabetes insipidus (▶ Chap. 9) and the syndrome of inappropriate antidiuretic hormone secretion (SIADH, ▶ Chap. 10) are useful to read.

4

Take-Home Messages

- Non-functioning pituitary adenomas (NFPAs) are benign adenohypophyseal tumors not associated with clinical evidence of hormonal hypersecretion.
- NFPAs comprise different histological subtypes, classified according to their immunostaining to different adenohypophyseal hormones and transcription factors.
- A predominant part of NFPA produce *gonadotropins,* but are not able to secrete them into circulation (silent gonadotropinomas).
- Most of NFPAs are asymptomatic and are diagnosed incidentally on MRI or CT as pituitary incidentalomas.
- In macroadenomas the main symptoms resulting from the mass effect of the tumor are headache, visual disturbances, and pituitary hormone deficiency.
- The most frequent pituitary deficit is central hypogonadism, followed by secondary hypothyroidism and secondary adrenal insufficiency.
- Dynamic tests are recommended only if secondary adrenal insufficiency is suspected.
- Magnetic resonance imaging (MRI) of the sellar region with and without gadolinium contrast is the gold standard to evaluate NFPA.
- Treatment options for NFPAs include active observation, surgical treatment, and radiotherapy.
- Follow-up is individualized and should consider tumor size, prior treatments, and clinical symptoms.

Suggested Reading

1. Caimari F, Korbonits M. Novel genetic causes of pituitary adenomas. Clin Cancer Res. *2016*;22(*20*):5030–42. https://doi.org/10.1158/1078-0432.CCR-16-0452.
2. Castinetti F, Dufour H, Gaillard S, Jouanneau E, Vasiljevic A, Villa C, Trouillas J. Consensus. Non-functioning pituitary adenoma: when and how to operate? What pathologic criteria for typing? Ann Endocrinol. 2015;76:220–7. https://doi.org/10.1016/j.ando.2015.04.007.
3. Ceccato F, Regazzo D, Barbot M, Denaro L, Emanuelli E, Borsetto D, Rolma G, Alessio L, Gardiman MP, Lombardi G, Albiger N, D'Avella D, Scaroni C. Early recognition of aggressive pituitary adenomas: a single-centre experience. Acta Neurochir. 2018;160:49–55. https://doi.org/10.1007/s00701-017-3396-5.
4. Chanson P, Raverot G, Castinetti F, Cortet-Rudelli C, Galland F, Salenave S. Consensus. Management of clinically non-functioning pituitary adenoma. Ann Endocrinol. 2015;76:239–47. https://doi.org/10.1016/j.ando.2015.04.002.
5. Drummond JB, Ribeiro-Oliveira A, Soares BS (2018) Non-functioning pituitary adenomas. Endotext [Internet]. www.endotext.org. Last Update: 28 Nov.
6. Esposito D, Olsson DS, Ragnarsson O, Buchfelder M, Skoglund T, Johannsson G. Non-functioning pituitary adenomas: indications for pituitary surgery and post-surgical management. Pituitary. 2019;22(4):422–34. https://doi.org/10.1007/s11102-019-00960-0.
7. Freda PU, Beckers AM, Katznelson L, Molitch ME, Montori VM, Post KD, Vance ML. Endocrine Society. Pituitary incidentaloma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(4):894–904. https://doi.org/10.1210/jc.2010-1048.
8. Galland F, Vantyghem M-C, Cazabat L, Boulinm A, Cotton F, Bonneville J-F, Jouanneau E, Vidal-Trécan G, Chanson F. Consensus. Management of nonfunctioning pituitary incidentaloma. Ann Endocrinol. 2015;76:191–200. https://doi.org/10.1016/j.ando.2015.04.004.
9. Liu J, He Y, Zhang X, Yan X, Huang Y. Clinicopathological analysis of 250 cases of pituitary adenoma under the new WHO classification. Oncol Lett. 2020;19(3):1890–8. https://doi.org/10.3892/ol.2020.11263.
10. Manojlovic-Gacic E, Engström BE, Casar-Borota O. Histopathological classification of non-functioning pituitary neuroendocrine tumors. Pituitary. 2018;21(2):119–29. https://doi.org/10.1007/s11102-017-0855-1.
11. Melmed S. Pituitary-tumor endocrinopathies. N Engl J Med. 2020;382:937–50. https://doi.org/10.1056/NEJMra1810772.
12. Mercado M, Melgar V, Salame L, Cuenca D. Clinically non-functioning pituitary adenomas: Pathogenic, diagnostic and therapeutic aspects.

Endocrinol Diabetes Nutr. 2017;64(7):384–95. https://doi.org/10.1016/j.endinu.2017.05.009.
13. Molitch ME. Diagnosis and treatment of pituitary adenomas. A review. J Am Med Assoc. 2017;317(5):516–24. https://doi.org/10.1001/jama.2016.19699.
14. Ntali G, Wass JA. Epidemiology, clinical presentation and diagnosis of non-functioning pituitary adenomas. Pituitary. 2018;21(2):111–8. https://doi.org/10.1007/s11102-018-0869-3.
15. Raverot G, Assié G, Cotton F, Cogne M, Boulin A, Dherbomez M, Bonneville J-F, Massart C. Consensus. Biological and radiological exploration and management of non-functioning pituitary adenoma. Ann Endocrinol. 2015;76:201–9. https://doi.org/10.1016/j.ando.2015.04.005.

Craniopharyngioma

Réka Kollár and Nikolette Szücs

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_5

Opening

In this chapter we will discuss the clinical features, diagnosis, and treatment of craniopharyngiomas that are tumors located in the sellar region, but do not originate from cells of the pituitary, but from the remnants of the Rathke's pouch.

5

Definition of the Disease

Craniopharyngioma is a histologically benign, solid or mixed solid, and cystic tumor that arises from the remnants of the Rathke's pouch along the line from the nasopharynx to the diencephalon. The tumor is localized mostly in the suprasellar region, but it can have an intrasellar component, too. Only 5–6% of the cases have only intrasellar localization. Histologically this tumor is referred to as a Rathke's pouch tumor or a hypophyseal duct tumor.

Craniopharyngiomas are rare tumors, having an incidence of around 1.3/1 million individuals per a year. The tumor has a bimodal distribution with a peak in childhood between 5 and 14 years of age and the second peak in adults between 50 and 75 years of age.

There are two types of craniopharyngiomas. Adamantinomatous craniopharyngioma occurs mostly in children, and it is often associated with somatic mutations in the *CTNNB1* gene coding for β-catenin. Papillary craniopharyngiomas, on the other hand, are more common in adults and are typically associated with somatic mutations of the *BRAF* oncogene.

Despite being histologically benign and not giving metastases, due to their localization and invasive behavior, craniopharyngiomas can be associated with severe clinical complications.

Case Presentation

A 38-year-old male patient was complaining about decreased libido, weight gain, blurry vision, and partial vision loss. Ophthalmological investigation revealed a lower temporal scotoma and bitemporal hemianopsia. Subsequent sella MRI showed a suprasellar, 28 × 20 × 20 mm structure with two big and several smaller cysts.

The tumor was fully removed via a transsphenoidal intervention, and the histology confirmed craniopharyngioma. The patient was referred to our center after surgery for a postoperative hormonal evaluation.

What can be suspected based on the symptoms of the patient?

Both mass effects of a large pituitary tumor manifesting itself in blurry vision and visual field defects and also signs of hypopituitarism can be suspected. Decreased libido and weight gain can be signs of secondary (hypogonadotropic) hypogonadism.

The diagnosis of craniopharyngioma cannot be suspected based on the symptoms. The symptoms are only characteristic for a pituitary mass, but its etiology cannot be suspected based on the symptoms only.

Craniopharyngiomas are slowly growing tumors. Symptoms are usually present for a year or more before the diagnosis is established.

Visual symptoms are frequent in patients with craniopharyngioma, due to the compression of the optic chiasm or both optic nerves. This can lead

to blurry vision, decreased visual acuity, or even visual field defects including the typical bitemporal hemianopsia. In severe cases, even blindness can occur. Headaches are present in more than 50% of patients that can be related to the traction of pain-sensitive structures by the tumor, or to obstructive hydrocephalus from tumor compression of the third ventricle. Similarly to other suprasellar tumors, large lesions can result in other severe neurological complications such as cranial nerve palsies, invasion of the cavernous sinus, increased intracranial pressure, etc.

What kind of endocrine disturbances can occur due to a craniopharyngioma?

Craniopharyngioma is always inactive hormonally, as it is not a tumor deriving from the pituitary itself. Its hormonal consequences are related to mass effects including the suppression of normal pituitary functioning; thus deficiencies in pituitary hormones and even panhypopituitarism can occur.

The symptoms and presentation of hypopituitarism caused by a craniopharyngioma do not differ from other causes of hypopituitarism (detailed in the next ► Chap. 6 on hypopituitarism).

The most frequent hormonal alteration is the deficiency of growth hormone (GH) that is observed in 75% of the cases.

Deficiency in gonadotropins, TSH, and ACTH can also occur.

Reduction in prolactin (PRL) production is uncommon in craniopharyngioma. Large craniopharyngiomas can paradoxically elevate blood PRL levels due to pituitary stalk compression.

What did the preoperative hormone panel show?

A basal preoperative hormone testing should at least include measurements for thyroid (TSH, fT4) and adrenal functioning (serum cortisol), but other pituitary axes including GH/IGF-1, gonadotropins, testosterone/estradiol, and prolactin can also be measured. The preoperative hormone panel for our patient (taken at another institution) showed a normal morning cortisol (15.16 µg/dL, normal range, 8.00–25.00), a normal TSH (0.716 mIU/L, normal range, 0.35–4.940), mildly elevated prolactin (31.69 ng/mL, normal range, 1.20–10.70), and severely reduced total testosterone (0.60 ng/mL, normal range, 2.80–8.00). Unfortunately, no fT4, LH, and FSH were done. The mild elevation of prolactin could be the result of a pituitary stalk lesion.

Which imaging techniques can be used for craniopharyngioma, and what are the typical imaging features?

As for pituitary imaging, sella MRI is the technique of choice for visualizing craniopharyngioma. Computed tomography (CT) can also be helpful to detect the calcification of the tumor. Cysts and solid components of the tumor can be visualized by both techniques.

In our case, sella MRI scan showed a suprasellar tumor, ventral from the chiasma opticum that was 28 × 20 × 20 mm large with two bigger and several smaller thin-walled cysts. Near the cysts's meeting points, an inhomogeneous 10 × 12 × 10 mm solid component was described. The surrounding cerebral tissue, hypothalamus, thalamus, and corpus mamillare were compressed and dislocated by the tumor. The caudal part of pituitary stalk was deviated to the right. The chiasma was dislocated dorsally, and its left ventral side was thickened (■ Fig. 5.1a, b).

What are the differences between adamantinomatous and papillary craniopharyngioma on imaging?

Adamantinomatous craniopharyngioma has cauliflower-like shape appearance

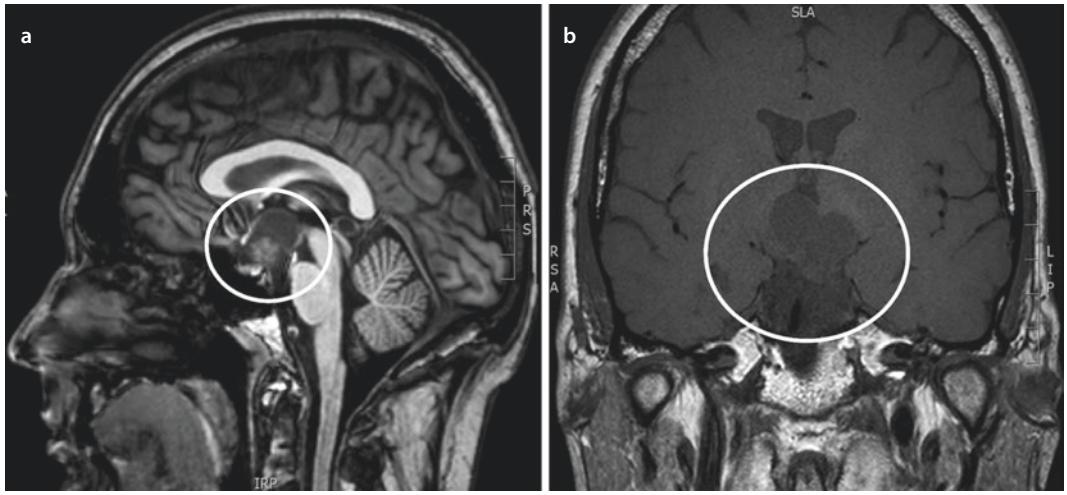

Fig. 5.1 T1-weighted MRI showing the tumor in circle on a sagittal **a** and coronal **b** section

on MRI with 90% calcifications and 90% cysts which contain cholesterol-rich oily fluid. Papillary craniopharyngiomas on sella MRI are typically solid tumors that are rarely cystic without calcifications.

What is the treatment of choice for craniopharyngioma?

The first-line treatment is neurosurgical intervention, which is indicated in almost all cases. The goal is to remove as much tumor as possible and to diminish the mass-related symptoms.

In patients with large cystic tumor components, preoperative cyst aspiration can be performed to reduce the mass effect or to relieve obstructive hydrocephalus.

The second-line treatment option is radiotherapy (RT) that is mainly used in patients with residual disease after a partial neurosurgical resection.

In our case, the craniopharyngioma was removed via a transsphenoidal route, and the histological examination revealed an adamantinomatous craniopharyngioma which is relatively rare in adults.

What kind of complications can we expect postoperatively?

Deficiencies for various pituitary hormones and even panhypopituitarism can develop postoperatively. Moreover, hypothalamic dysfunction might also arise that can lead to severe obesity, sleep disorders, diabetes insipidus, or problems with temperature regulation (mainly hyperthermia). Visual disturbances can be aggravated by surgery or RT. Patients with craniopharyngioma have an increased risk for cerebrovascular hemorrhage or ischemic cerebrovascular disease. The use of RT has been associated with secondary cerebral malignancies like meningioma or malignant glial tumors.

Case Continued

Postoperative hormonal evaluation is warranted in every patient operated for craniopharyngioma. Table 5.1 presents the results of the postoperative hormone panel. The hormone panel shows secondary adrenal insufficiency (low cortisol and ACTH), secondary hypothyroidism (low TSH and fT4), and secondary (hypogonadotropic) hypogonadism (low gonadotropins, low free and total testosterone with normal SHBG). The patient also reported polydipsia and polyuria due to diabetes insipidus. Desmopressin was started along with treatment for adrenal insufficiency and central hypothyroidism (hydrocortisone and levothyroxine, respectively), and the patient later also received testosterone substitution.

The treatment for hypopituitarism and diabetes insipidus is the same as in other settings.

Table 5.1 Postoperative hormone findings in the patient's case

Hormone	Value	Unit	Normal range
Serum cortisol	4.58	μg/dL	8.00–25.00
Plasma ACTH	1.04	pg/mL	5.0–60.0
TSH	0.172	mIU/L	0.35–4.940
fT4	10.00	pmol/L	9.00–23.00
FSH	0.11	IU/L	1.5–12.4
LH	0.03	IU/L	1.7–8.6
PRL	62.23	ng/mL	1.20–10.70
Free testosterone	6.80	pg/mL	100.00–500.00
Total testosterone	0.27	ng/mL	2.80–8.00
SHBG	41	nmol/L	11.3–52.3

SHBG sex hormone-binding globulin

Tips

The reader is advised to read the chapter on non-functioning pituitary adenoma, the next chapter on hypopituitarism, and the chapter on diabetes insipidus.

Take-Home Messages

- Craniopharyngioma is a benign, rare solid or mixed solid, and cystic tumor of the sellar region.
- The suspicion of craniopharyngioma can be raised by its typical imaging features (MRI or CT), and its diagnosis is confirmed by histology.
- Its primary treatment is surgical. Irradiation therapy can be used as second line.
- Postoperative hypopituitarism occurs in most patients.

Suggested Reading

1. Dandurand C, Sepehry AA, Asadi Lari MH, Akagami R, Gooderham P. Adult craniopharyngioma: case series, systematic review, and meta-analysis. Neurosurgery. 2018;83(4):631–41. https://doi.org/10.1093/neuros/nyx570.
2. Garnett MR, Puget S, Grill J, Sainte-Rose C. Craniopharyngioma. Orphanet J Rare Dis. 2007;2:18. https://doi.org/10.1186/1750-1172-2-18.

3. Garrè ML, Cama A. Craniopharyngioma: modern concepts in pathogenesis and treatment. Curr Opin Pediatr. 2007;19:471–9. https://doi.org/10.1097/mop.0b013e3282495a22.
4. Honegger J, Tatagiba M. Craniopharyngioma surgery. Pituitary. 2008;11:361. https://doi.org/10.1007/s11102-008-0137-z.
5. Jane JA Jr, Laws ER. Craniopharyngioma. Pituitary. 2006;9:323. https://doi.org/10.1007/s11102-006-0413-8.
6. Koutourousiou M, Fernandez-Miranda JC, Wang EW, Snyderman CH, Gardner PA. The limits of transsellar/transtuberculum surgery for craniopharyngioma. J Neurosurg Sci. 2018;62:301–9. https://doi.org/10.23736/S0390-5616.18.04376X.
7. Lober RM, Harsh GR 4th. A perspective on craniopharyngioma. World Neurosurg. 2013;79:645–6. https://doi.org/10.1016/j.wneu.2012.10.064.
8. Müller HL, Merchant TE, Warmuth-Metz M, Martinez-Barbera JP, Puget S. Craniopharyngioma. Nat Rev Dis Primers. 2019;5(1):75. https://doi.org/10.1038/s41572-019-0125-9.

Hypopituitarism

Nikolette Szücs

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_6

Opening

In this chapter the reader will be informed about the specific clinical features, diagnosis and treatment of pituitary insufficiency, in other words hypopituitarism.

Definition of the Disease

The pituitary gland is the main regulatory organ of the endocrine system that consists of two lobes: the anterior lobe (adenohypophysis) which produces ACTH (adrenocorticotropic hormone), TSH (thyroid-stimulating hormone), LH (luteinizing hormone), FSH (follicle-stimulating hormone), GH (growth hormone), and PRL (prolactin) and the posterior lobe where antidiuretic hormone (ADH)/vasopressin and oxytocin produced by hypothalamic cells are stored.

Hypopituitarism is a rare condition characterized by the complete or partial absence of one, or more, or all of the hormones in the anterior lobe of pituitary gland that is sometimes associated with the absence of hormones of the posterior lobe, as well. (The deficiency of ADH leads to central (neurohypophyseal) diabetes insipidus that is discussed in ► Chap. 9, whereas no clinical signs have been associated with oxytocin deficiency to date.)

The term panhypopituitarism refers to the clinical condition if most or all pituitary hormones are lacking.

The clinical manifestations of the disease are greatly dependent on the etiology and severity of the hormone deficiency, age of the patient, and duration of disease.

Hypopituitarism can be reversible or permanent, congenital or acquired, and sporadic or familiar.

Treatment and prognosis depend on the extent of hypofunction and the causes of the disease.

The explicit incidence of hypopituitarism is unknown, but it is estimated at 5–50 cases per 100,000, with occurrences identified in both sexes.

Case Report

A 57-year-old man was referred to our endocrinological consultation because of decreased libido, reduced facial and body hair, weight loss, headache, and general fatigue (Fig. 6.1). He complained of dizziness especially when standing up.

His blood pressure was low (90/60 mmHg), and orthostatic hypotension was observed.

A previously performed laboratory test has shown discrete normocytic anemia, a mild hyponatremia (131 mmol/L, normal serum Na^+, 135–145 mmol/L) elevated cholesterol levels, and normal TSH and low fT4 (free L-thyroxine) levels.

Ophthalmological examination confirmed bitemporal hemianopsia.

Fig. 6.1 Portrait of the patient. Note the fine wrinkles of the skin and lack of facial hair that are typical features of hypopituitarism in males

What are the characteristics of this case that make us suspect the possibility of a pituitary disease?

Headache, general fatigue, hypotension, the signs of hypogonadism, and the visual disturbance raise the possibility of a pituitary pathology.

Sella MRI (magnetic resonance imaging) showed a large intra- and suprasellar tumor (Fig. 6.2).

What can be inferred from the baseline hormone levels presented in Table 6.1?

All hormone levels except TSH are low. The pattern of such hormone alterations is characteristic for secondary hormone deficiencies that are caused by the lack of pituitary hormones (ACTH, TSH, LH, FSH). Low ACTH and cortisol stands for secondary adrenal insufficiency, low gonadotropins (LH, FSH), and low testosterone for secondary (hypogonadotropic) hypogonadism. In secondary hypothyroidism, TSH can be low or normal, but fT4 is invariably low.

What is the difference between primary, secondary, and tertiary insufficiencies?

In the hypothalamic-pituitary-(adrenal, thyroid, gonad) axes, the defects at the different levels lead to different hormonal constellations. In primary insufficiencies (primary adrenal insufficiency, primary hypothyroidism, and primary hypogonadism), the end organ is failing, and the feedback regulation by the end hormone product (cortisol, thyroxine, or sex steroid (testosterone, estradiol)) is not working. The pituitary therefore increases the secretion of ACTH, TSH, and gonadotropins, respectively. In contrast, in secondary insufficiencies, the disease affects the pituitary, and therefore both pituitary hormones and the end products will be low. Tertiary insufficiency refers to rare hypothalamic problems.

Table 6.1 Baseline hormone levels

Hormone	Value	Normal range
Cortisol	0.3 µg/dL	8.0–25.0
ACTH	0.1 pg/mL	7.2–63.3
LH	0.4 mIU/mL	1.3–11.8
FSH	0.8 mIU/mL	1.3–11.8
IGF-1	53.0 ng/mL	92.7–244.6
GH	0.1 ng/mL	0.0–6.0
Total testosterone	30.0 ng/dL	300.0–800.0
TSH	1.92 mIU/L	0.4–4.9
Free T4	0.65 ng/dL	0.70–1.80

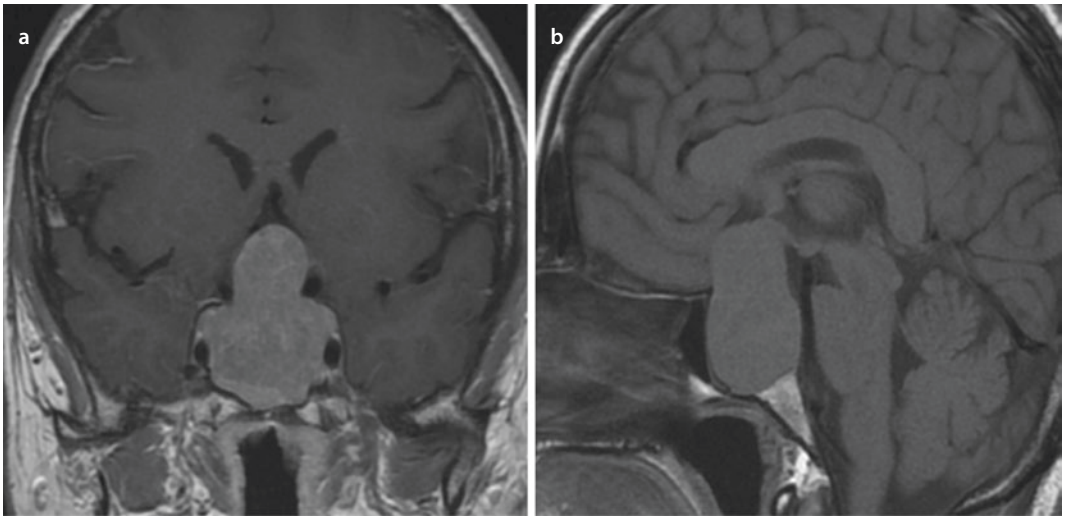

Fig. 6.2 Large pituitary tumor with intra- and suprasellar propagation on T1-weighted MRI (coronal **a** and sagittal **b** slice)

Case Presentation Continued

Hydrocortisone and levothyroxine substitution was introduced before the neurosurgical intervention.

The tumor was fully removed by transsphenoidal operation, and the histology confirmed a chromophobe adenoma with a Ki-67 proliferation index of 1–2%.

What can cause hypopituitarism?

Many medical conditions that disturb the normal interaction between the hypothalamus and the pituitary gland can cause hypopituitarism.

The most common causes of hypopituitarism in adults are pituitary or parasellar tumors and their treatment (Table 6.2).

Nowadays, the incidence of pituitary injury is increasing that can be related to a growing number but also increasing awareness of traumatic brain injury and cranial irradiation.

Infiltrative diseases such as histiocytosis, sarcoidosis, and haemochromatosis can cause hypopituitarism as part of the systemic disease.

Pituitary apoplexia may occur in pituitary adenoma, mostly in macroadenomas.

Lymphocytic hypophysitis (detailed in the chapter on hypophysitis) is another major cause of hypopituitarism. Hypophysitis can manifest itself during pregnancy or after delivery, as well.

The recently developed cancer immunotherapies against immune checkpoints (immune checkpoint inhibitors) can cause an acute and rapidly developing hypophysitis, which can be associated with severe hypopituitarism (detailed in the chapter on hypophysitis, ▶ Chap. 8).

Table 6.2 Etiology of hypopituitarism

Neoplastic/ compression	Pituitary tumor
	Metastases
	Craniopharyngioma
	Cyst (Rathke's cleft, arachnoid)
	Meningioma
	Glioma
	Germinoma
	Empty sella
Treatment of sellar lesions	Surgery
	Radiation therapy
Traumatic	Traumatic brain injury
Vascular	Apoplexy
	Aneurysm
	Sheehan syndrome
	Subarachnoid hemorrhage
Infiltrative/ inflammatory	Hypophysitis (autoimmune)
	Sarcoidosis
	Haemochromatosis
	Histiocytosis X
Infectious	Tuberculosis
	Bacterial, fungal
Genetic mutations	HESX1, PROP1, LHX3/ LHX4 PIT-1
Functional	Anorexia nervosa
	Extreme physical activity
Idiopathic	

Hypopituitarism can be sometimes associated with the empty sella syndrome that is a radiological term describing the herniation of subarachnoid space into the sellar cavity. It can be idiopathic or occur secondarily to a treated pituitary tumor (Fig. 6.3).

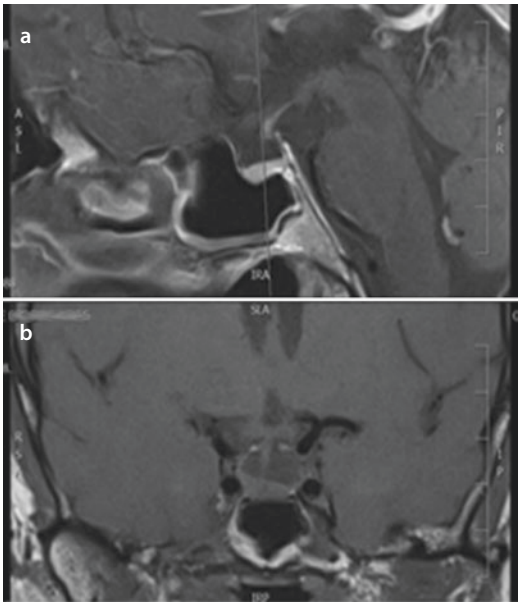

Fig. 6.3 Idiopathic empty sella on a T1-weighted MRI (sagittal **b** and coronal **a** slices)

What is Sheehan syndrome?

Rarely, pituitary apoplexia may occur in the normal pituitary gland during or after delivery (postpartum pituitary hemorrhage). Lack of breast milk production can be the first sign, but due to the deficiency of other adenohypophyseal hormones, further symptoms of hypopituitarism might also develop (in severe cases even cachexia).

Which hormone is usually lost first in the progression of hypopituitarism?

GH is usually the first hormone to be deficient, then the gonadotropins (LH, FSH), followed by TSH, and the last is usually ACTH (not considering prolactin). This sequence appears to be similar to the physiological importance of these hormones. It must be noted, however, that this is only a general sequence, and individual cases may be quite variable. Isolated hormone deficiencies also occur.

What are the common signs and symptoms associated with adult hypopituitarism?

Deficiency of ACTH (secondary adrenal insufficiency) is the most serious problem of anterior pituitary hormone deficit. ACTH deficiency is characterized by general fatigue, weight loss, recurrent nonspecific abdominal pain, hyponatremia, hypoglycemia, and orthostatic hypotension. Adrenal crisis may develop with severe hyponatremia, hypotonia, and hypovolemia during an intercurrent illness. (More details in ▶ Chap. 31 on Addison's disease and autoimmune polyendocrine syndrome type 2.) The pigmentation – which is a typical sign in primary adrenal failure – is absent.

The signs and symptoms with TSH deficiency (secondary hypothyroidism) are practically analogous to those of primary hypothyroidism (cold intolerance, weight gain, dry skin, general fatigue, memory disorder) (presented in ▶ Chap. 11), but in contrast to primary hypothyroidism, the atrophy of thyroid gland can occur.

GH deficiency in childhood results in short stature. In adults, GH deficiency is related to abnormal body composition: increased fat mass increased and reduced lean body mass primarily due to increased intra-abdominal or visceral fat deposition. Deficiency for GH has also been related to low bone mineral density. Elevated carotid intima media thickness and C-reactive protein, LDL cholesterol, and insulin resistance can increase cardiovascular mortality. Altogether, deficiency for GH contributes to an impaired quality of life in these patients.

The clinical symptoms of gonadotropin deficiency are determined by the gender and age in which the condition develops. In adult males, body and facial hair may be lost, libido and fertility may be reduced, and erectile dysfunction is also common.

Testosterone deficiency can lead to non-specific symptoms, like reduced exercise capacity, general fatigue, and reduced muscle mass. In contrast to men, where the symptoms are not so conspicuous, the oligo-amenorrhea in women can be the first sign of the disease, and therefore the diagnosis might be earlier. Pubic and axillary hair grow thinner, and hot flushes, vaginal dryness, and breast atrophy can occur. In both genders bone mineral density decrease, osteopenia and osteoporosis can be detected, and fracture risk is elevated.

As it is evident from the above, the symptoms related to various hormone deficiencies overlap. Almost all hormone deficiencies contribute to weakness, fatigue, and reduced quality of life. Hyponatremia is related to both ACTH and TSH deficiencies. Both gonadotropin and GH deficiencies contribute to reduced BMD.

Table 6.3 presents the common signs and symptoms in hypopituitarism.

Is it necessary to perform hormone tests again after the operation?

Yes, because some hormones may return to normal after surgery due to the resolution of tumor-induced compression on the pituitary. Unfortunately, however, it is also common that additional pituitary hormone deficiencies develop after the intervention.

Back to Our Patient

Following the transsphenoidal adenomectomy, the visual disturbance has been solved, but the repeated hormone tests showed no change in the hormone results, thus confirming panhypopituitarism. In addition to hydrocortisone and thyroxine replacement, testosterone replacement was started, as well.

Daily fluid turnover was normal.

What kind of hormone tests can be necessary for the diagnosis of hypopituitarism?

In most patients, it is sufficient to take basal serum hormone level, but for the patients with questionable, borderline cases, dynamic endocrine testing is recommended. As shown in Table 6.1, the basal levels of all adenohypophyseal hormones were low in our patient; therefore the diagnosis in this case is clear-cut.

Table 6.3 Common signs and symptoms in pituitary insufficiency

Hormone deficiency	Related symptoms
ACTH	Weakness, tiredness, dizziness on standing, pallor, hypoglycemia, weight loss, hyponatremia
TSH	Weight gain, fatigue, decreased mental function, constipation, bradycardia, cold intolerance, dry skin, thyroid gland atrophy
Gonadotropins (LH, FSH)	Adolescence: delayed puberty In adult women: oligo-amenorrhea, infertility, dyspareunia, regression of secondary sexual characteristics, (reduced axillary and pubic hair, breast atrophy), decreased BMD In man: poor libido, impotence, infertility, regression of secondary sexual characteristics (reduced facial/body hair, small soft testes) decreased BMD
GH	Short stature in children In adults: fatigue, abnormal body composition, muscle mass and muscle energy are reduced, physical tolerability is reduced, muscle/fat ratio decreases, cardiovascular risk increased, "well-being" and performance reduced, tendency for depression, social isolation, decreased BMD
Prolactin	Lack of lactation after childbirth

- Regarding ACTH deficiency, a morning serum cortisol level lower than 3 μg/dL (80 nmol/L) is usually characteristic for adrenal insufficiency. Dynamic tests can be helpful for the diagnosis of ACTH deficiency that include the short ACTH test (cosyntropin, tetracosactide 250 μg) and the insulin tolerance test.

- TSH deficiency is confirmed if free thyroxine (fT4) level is low along with a low or normal TSH.

- Low LH, FSH levels with decreased morning testosterone or estradiol concentrations verify gonadotropin deficiency (secondary hypogonadism).

- PRL deficiency can be defined when patient has low or undetectable serum PRL level.

- If more than three other pituitary hormones are deficient and the gender and age-adjusted insulin-like growth factor-1 (IGF-1) level is below the lower limit of normal, GH deficiency can be confirmed. Otherwise, the low GH and IGF-1 measurement is not sensitive enough, and provocative GH tests, insulin tolerance test, GHRH (growth hormone-releasing hormone)+arginine, macimorelin (ghrelin receptor agonist), or glucagon stimulation, are required.

What is the rationale to perform an ACTH-test for the diagnosis of ACTH-deficiency?

- ACTH is a trophic factor for the adrenal gland. In case of ACTH deficiency, an atrophy of the adrenal cortex develops within some weeks, and the ACTH stimulation will not provoke an adequate cortisol response. The ACTH test will not be positive within 3–4 weeks after the event (e.g., pituitary surgery) responsible for hypopituitarism.

How is the ACTH-test performed?

- 250 μg tetracosactide (ACTH analogue) is injected intravenously, and blood is drawn 30 and/or 60 minutes later. A normal response is seen, if cortisol is higher than 18 or 20 μg/dL (500 or 540 nmol/L) either at baseline or after stimulation. (A low-dose ACTH test including 1 μg tetracosactide has also been developed, and some authors consider it better than the standard high dose with 250 μg to diagnose secondary adrenal insufficiency. However, it is not widespread and not available commercially.)

What is the rationale of insulin-induced hypoglycemia test (insulin tolerance test (ITT))?

- Hypoglycemia is a major stress situation, and thereby both ACTH and cortisol are stimulated. If their stimulation is unsatisfactory, the diagnosis of secondary adrenal insufficiency can be confirmed. GH is also induced, and therefore the test is also used in the diagnosis of GH deficiency.

- 0.1–0.15 IU/kg regular fast-acting insulin is injected intravenously, and blood is drawn every 15 minutes till 60 minutes and also during hypoglycemia that should be judged clinically based on the typical symptoms (neuroglycopenia and adrenergic symptoms). Hypoglycemia during ITT is defined as a serum glucose below 2.2 mmol/L (40 mg/dL). Cortisol usually increases over 20 μg/dL (540 nmol/L) during hypoglycemia, and ACTH is usually higher than 150 pg/mL (33 pmol/L). The dynamics of cortisol and ACTH change is important.

- Regarding GH, a peak GH below 3 ng/mL in adults is defined as severe deficiency. (The cutoff for peak GH during provocative tests in children is higher (7 ng/mL), and therefore milder cases of GH deficiency can also warrant treatment in children.)

Is there any risk of insulin-induced hypoglycemia?

Yes, it should not be performed in patients with cardiac/cerebrovascular disease or epilepsy. The test is certainly unpleasant and requires continuous monitoring, and therefore some centers prefer alternative dynamic tests.

What is the metyrapone test?

Metyrapone is an inhibitor of the 11β-hydroxylase enzyme catalyzing the final step of cortisol biosynthesis, and it is therefore exploited in the therapy of hypercortisolism (Cushing's syndrome). Metyrapone can also be used to investigate the ACTH secretion of the pituitary (ACTH reserve). Metyrapone is taken at midnight at a dose of 30 mg/kg, and blood is drawn the next morning for 11-deoxycortisol (the steroid product before the enzymatic step catalyzed by 11β-hydroxylase) and cortisol. 11-Deoxycortisol below 7 μg/dL can indicate deficiency in ACTH. The test is, however, rarely used nowadays despite being an alternative to invasive ITT for assessing the hypothalamic-pituitary-adrenal axis.

How should hypopituitarism be treated?

We should substitute the end products of the hormone axes and not the pituitary hormones except for GH. Since the adenohypophyseal hormones are proteins, their substitution would require parenteral injections; moreover the half-lives of these proteins are also shorter than that of the hormonal end products.

Regarding ACTH deficiency, hydrocortisone corresponding to normal adrenocortical cortisol is given. The daily total 15–20 mg hydrocortisone dose should be given in two or three parts: the highest dose in the morning, second in the afternoon, and third – if necessary – in the evening. In contrast to primary adrenal insufficiency (Addison's disease), mineralocorticoid substitution (fludrocortisone) is not necessary, as aldosterone production is not primarily regulated by ACTH.

In emergency and stress situations, the dose of hydrocortisone should be increased (see the chapter on Addison's disease and autoimmune polyendocrine syndrome type 2 for more details on glucocorticoid replacement, ▶ Chap. 31).

Unfortunately, there is no specific marker for monitoring the glucocorticoid replacement therapy in secondary adrenal insufficiency; only the clinical conditions can give appropriate feedback. (In contrast, in primary adrenal insufficiency, where ACTH is high without treatment, the reduction in ACTH can be helpful for monitoring.)

The dose of levothyroxine replacement may vary between 50 and 200 μg per day. The aim is to achieve serum fT4 levels in the mid- to upper half of the reference range. In contrast with primary hypothyroidism, where TSH is a very good marker of levothyroxine substitution, in secondary hypothyroidism TSH cannot be used for monitoring; only fT4 levels are informative.

The treatment strategies for hypogonadotropic hypogonadism are detailed in the next chapter on Kallmann syndrome.

Back to Our Patient

12 months after the transsphenoidal operation, the control MRI didn't show any residual tumor (Fig. 6.4).

As the patient was deficient in more than three pituitary hormones, the deficiency for GH could be established based on the low IGF-1 level without a stimulation test. Human recombinant GH treatment was introduced in a dose of 0.3 mg sc. daily.

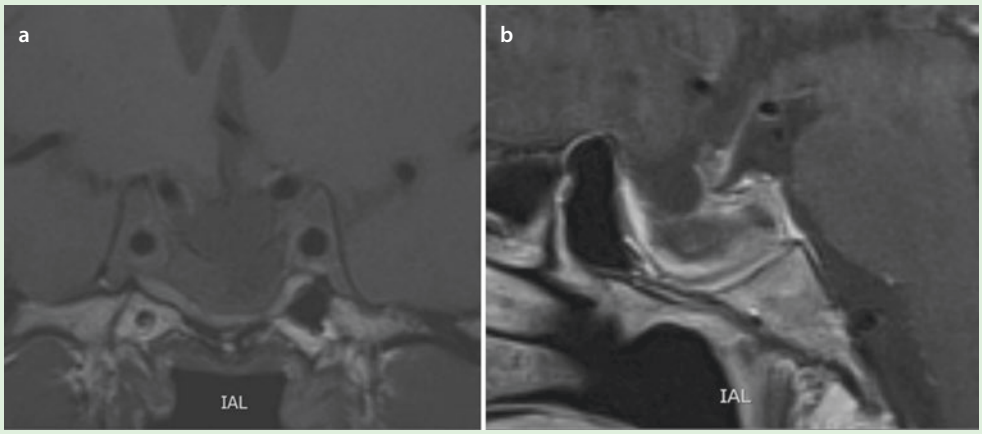

Fig. 6.4 No residual tumor 12 months after the operation on T1-weighted MRI (coronal **a** and sagittal **b** slice)

How should GH replacement be initiated?

Due to the common side effect of GH associated with fluid retention, initially low dose (0.2–0.3 mg) GH replacement is preferred. Younger patients and women (especially receiving oral estrogens) require higher doses. Serum IGF-1 should be monitored every 3 months to establish the optimal dose.

Is there an order in which hormone replacement therapy should be introduced?

Yes, if glucocorticoid deficiency exists, treatment should be initiated with glucocorticoid replacement, followed by levothyroxine replacement and finally sex hormones. It is very important not to give levothyroxine before hydrocortisone administration, since thyroid hormones accelerate steroid hormone metabolism and thereby could precipitate an adrenal crisis.

Growth hormone replacement therapy can be initiated only in a patient with stable, well-treated hypopituitarism, as a final step of the complex treatment protocol.

Is there any contraindication to GH treatment?

Yes, the GH replacement is contraindicated in active malignancies, diabetic retinopathy, benign intracranial hydrocephalus, and growing residual pituitary tumors.

Do patients need life-long care?

Patients who suffer from hypopituitarism require continued follow-up visits – initially every 3 months – and with stable, well-controlled conditions in 6 months or in yearly intervals.

Tips

This chapter on hypopituitarism is one of the most comprehensive chapters in this book. The reader is advised to read the chapter on non-functioning pituitary adenoma (▶ Chap. 4), the following chapter on Kallmann syndrome (▶ Chap. 7), hypophysitis (▶ Chap. 8), and diabetes insipidus (▶ Chap. 9). As the symptoms of primary and secondary insufficiencies overlap, it is also helpful to read the chapters on

hypothyroidism and Hashimoto's thyroiditis (▶ Chap. 11), Addison's disease, and polyendocrine autoimmune syndrome type 2 (▶ Chap. 31). The issues of glucocorticoid replacement are discussed in detail in the chapter on Addison's disease. The treatment of hypogonadotropic hypogonadism is discussed in the next chapter on Kallmann syndrome.

Take-Home Messages

- Hypopituitarism is a rare condition characterized by the complete or partial absence of one, or more, or all of the hormones in the anterior lobe of pituitary gland that is sometimes associated with the absence of hormones of the posterior lobe, as well.
- The clinical manifestations of the disease are greatly dependent on the etiology and severity of the hormone deficiency, age of the patient, and duration of disease.
- The treatment and prognosis of hypopituitarism depend on the extent of hypofunction and the causes of the disease.
- The treatment is based on well-structured hormone replacement therapy, which – in most cases – requires lifelong follow-up.

Suggested Reading

1. Arima H, Iwama S, Inaba H, Ariyasu H, Makita N, Otsuki M, Kageyama K, Imagawa A, Akamizu T. Management of immune-related adverse events in endocrine organs induced by immune checkpoint inhibitors: clinical guidelines of the Japan Endocrine Society. Endocr J. 2019;2866(7):581–6. https://doi.org/10.1507/endocrj.EJ19-0163.
2. Crowley RK, Argese N, Tomlinson JW, Stewart PM. Central hypoadrenalism. JCEM. 2014;99(11):4027–36. https://doi.org/10.1210/jc.2014-2476.
3. Fleseriu M, Hashim IA, Karavitaki N, Melmed S, Murad MH, Salvatori R, Samuels MH. Hormonal replacement in hypopituitarism in adults: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2016;101(11):3888–921. https://doi.org/10.1210/jc.2016-2118.
4. Higham CE, Johannsson G, Shalet SM. Hypopituitarism. Lancet. 2016;388(10058):2403–15. https://doi.org/10.1016/S0140-6736(16)30053-8.
5. Molitch ME, ClemmonsD R, Malozowski S, Merriam GR, Vance ML. Endocrine society evaluation and treatment of adult growth hormone deficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(6):1587–609. https://doi.org/10.1210/jc.2011-0179.
6. Persani L. Central hypothyroidism: pathogenic, diagnostic, and therapeutic challenges. JCEM. 2012;-97(9):3068–78. https://doi.org/10.1210/jc.2012-1616.
7. Stochholma K, Johannsson G. Reviewing the safety of GH replacement therapy in adults. Growth Horm IGF Res. 2015;25:149–57. https://doi.org/10.1016/j.ghir.2015.06.006.
8. Tanriverdi F, Dokmetas HS, Kebapcı N, Kilicli F, Atmaca H, Yarman S, Ertorer ME, Erturk E, Bayram F, Tugrul A, Culha C, Cakir M, Mert M, Aydin H, Taskale M, Ersoz N, Canturk Z, Anaforoglu I, Ozkaya M, Oruk G, Hekimsoy Z, Kelestimur F, Erbas T. Etiology of hypopituitarism in tertiary care institutions in Turkish population: analysis of 773 patients from pituitary study group database. Endocrine. 2014;47:198–205. https://doi.org/10.1007/s12020-013-0127-4.

Kallmann Syndrome (Hypogonadotropic Hypogonadism)

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Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_7

Opening

In this chapter, the reader will get acquainted with the clinical features, diagnosis, and treatment of Kallmann syndrome, a congenital form of hypogonadotropic hypogonadism.

Definition of the Disease

Kallmann syndrome is a rare form of congenital isolated GnRH (gonadotropin-releasing hormone) deficiency characterized by low serum gonadotropin levels and LH (luteinizing hormone) and FSH (follicle-stimulating hormone) levels and by consequent sex steroid deficiency. It occurs as in 10 in 100,000 boys and 2 in 100,000 girls.

The classic form is characterized by hypogonadotropic hypogonadism (lack of sexual maturity and absence of secondary sexual characteristics) with hyposmia or anosmia (decreased or absent smell) which is caused by failed migration of GnRH neurons from the olfactory placode into the brain (hypothalamus) during embryonic life.

Case Presentation

A 19-year-old man was admitted to our adult endocrinological consultation. His medical history included an orchidopexy due to undescended testis when he was half-year old. Unilateral renal agenesis was also detected by abdominal ultrasonography.

The diagnosis of central/hypogonadotropic hypogonadism was confirmed at the age of 13. The other pituitary hormone tests were normal.

An olfactory function test confirmed hyposmia.

Pituitary MRI was normal, without any defects of the olfactory tract.

What is the diagnosis of Kallmann syndrome based on?

For the diagnosis of Kallmann syndrome, clinical, hormonal, genetic, and imaging techniques can be used. Clinically, a lack of adolescence and signs of hypogonadism together with hyposmia/anosmia can raise suspicion.

The patient had undescended testis and unilateral renal agenesis, already diagnosed in infancy. His puberty was delayed, and during this period, hyposmia was diagnosed.

All these clinical features are typical in Kallmann syndrome.

The clinical symptoms in boys are lack of adolescence, absent facial and pubic hair growth, small testicles and penis, delayed growth spurt, eunuchoid body habitus (disproportionally long arms when compared to height), and decreased muscle mass.

In girls, the development of breasts is delayed, and delayed growth spurt, undergrown axillary and pubic hair, and primary amenorrhea can be observed.

What is the difference between primary and secondary/tertiary hypogonadism?

Primary hypogonadism is caused by a disease of the testicles (or ovaries in females), and therefore gonadotropins are elevated due to the feedback regulation of the "hypothalamic-pituitary-gonadal axis. Primary hypogonadism is therefore hypergonadotropic. On the other hand, secondary/tertiary hypogonadism is caused by pituitary or hypothalamic malfunctioning, respectively, and thus gonadotropins are low (hypogonadotropic). (Similar distinctions are valid for primary and secondary adrenal insufficiency and hypothyroidism, as well.)

Which hormone tests can be performed for evaluating Kallman syndrome?

As GnRH is not measurable, serum concentration of the gonadotropins (LH and FSH) and sex steroids are used for the diagnosis. Low LH and FSH, in men with low testosterone levels and in women with low estradiol and progesterone levels, are observed.

The hormone results in our case were LH, 0.4 IU/L (normal range, 1.7–8.6); FSH, 0.1 IU/L (normal range, 1.5–12.4); and total testosterone, 1.26 ng/mL (normal range, 2.8–8).

Is it worth doing a genetic assessment?

Mutations in more than 20 genes have been associated with Kallmann syndrome. The first responsible gene found was *KAL1* that is associated with an X-linked pattern of inheritance, and its mutations occur especially in men with unilateral renal agenesis and mirror movements – bimanual synkinesis. *FGR1 (KAL2)* mutations are inherited as autosomal dominant traits and are associated with midline facial abnormalities cleft lip or palate, dental agenesis, and short metacarpals and/or metatarsals.

In our case, the genetic testing confirmed a *KAL1* mutation.

Is imaging helpful in the diagnosis?

Radiographic imaging of the hypothalamus-pituitary region using MRI scans is recommended to explore any anatomical structural abnormalities (e.g., absence of olfactory structures), but the radiographic appearance of the hypothalamic-pituitary region is typically normal.

Are there other forms of hypogonadotropic hypogonadism apart from Kallmann syndrome?

Kallmann syndrome is the isolated hypogonadotropic hypogonadism form accompanied by anosmia or hyposmia.

Very similar signs and symptoms can be recognized in other forms of congenital isolated hypogonadotropic hypogonadism, but no smell dysfunction is detected in these. These congenital forms can be associated with mutations in the following genes: *GNRH1*, *KISS1*, *KISS1R (GPR54)*, *TAC3*, *TACR3*, etc.

How to treat hypogonadotropic hypogonadism?

In both sexes, the aim of the treatment is to induce puberty and later to maintain the normal sexual hormone levels, which sustain the secondary sexual characteristics.

For male patients, the goal of testosterone replacement therapies is to return serum testosterone levels into the physiological range. (Table 7.1).

Table 7.1 Medical treatment for puberty induction in boys, and maintenance treatment in male patients

T enanthate	Initial dose 50 mg i.m. monthly increasing every 6–12 months up to 250 mg/month
Gonadotropin	hCG 2 × 250 IU s.c. per week, increasing dose every 6 months up to 2–3 × 500 IU/weekly
	rFSH or hMG 75 IU/s.c. 2–3 times weekly
T enanthate	250 mg i.m. every 2–4 weeks
T undecanoate	1000 mg i.m. every 8–14 weeks
T gel	50–75 mg/day transdermally

T testosterone, *hCG* human chorionic gonadotropin, *hMG* human menopausal gonadotropin, *rFSH* recombinant human follicle-stimulating hormone

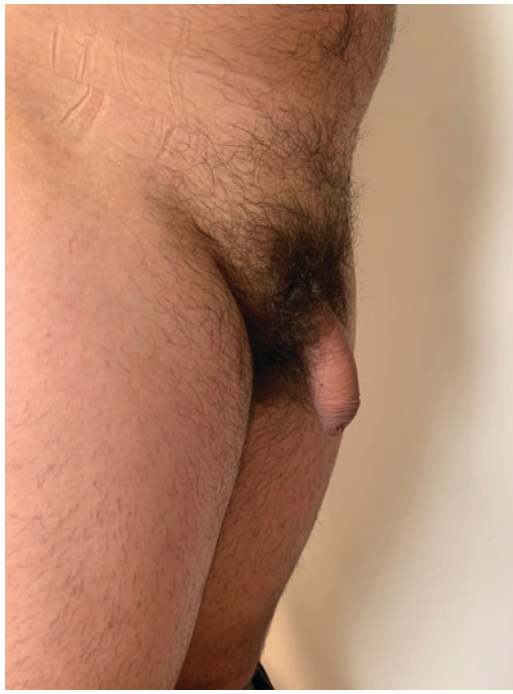

Fig. 7.1 Due to testosterone replacement, the penis size became normal, virilization was accomplished, but the size of testes remained small, about 4–6 ml

In our patient, testosterone replacement therapy by depot testosterone undecanoate every 12 weeks was introduced, and it resulted in the growth of the penis and development of secondary sexual characteristics (Fig. 7.1).

We can choose the daily transdermal form, which mimics the physiological secretion of testosterone, or the long-acting depot injection form, which can be more convenient for some patients.

For females, hormone replacement includes the usage of estrogen and progesterone. Firstly, estrogen is given in transdermal gel or tablet form, to maximize breast development, and then a combination of estrogen and cyclical progesterone is used to maintain the menstrual cycles and secondary sexual characteristics (Table 7.2).

Will patients treated with sexual steroids be fertile?

Table 7.2 Medical treatment of puberty induction and hypogonadism in female patients

17ß-Estradiol tablet	Initial dose 5 μg/kg daily increasing every 6–12 months up to 1–2 mg
17ß-Estradiol patch	Initial dose 0.05–0.07 μg/kg increasing every 6–12 months up to 50–100 μg/day
Progesterone tablet	Supplement after breast development 100–200 mg/day during 14 days in every month

No. Sexual steroids are only able to restore secondary sexual characteristics, but fertility will not be restored as gonadotropins are needed for the induction and maintenance of germ cell production. Figure 7.1 shows that the patient's testes remained small despite testosterone administration.

How to restore fertility in hypogonadotropic hypogonadism?

Fertility can be restored by adding GnRH or gonadotropins depending on the level of defect (hypothalamic or pituitary). GnRH can be given, if the pituitary is normally functioning. GnRH is usually given episodically by a pump mimicking its physiological release.

Gonadotropins can be given both to patients having dysfunctions in the hypothalamus or in the pituitary. For gonadotropin replacement, human chorionic gonadotropin (hCG) is usually given instead of LH. hMG is human menopausal gonadotropin that includes both FSH and LH bioactivity at an approximately 1:1 ratio.

Using gonadotropin therapy (hCG+hMG or recombinant FSH) fertility can be induced.

In our patient, hCG+hMG was used for 12 months, and it resulted in normal testosterone level. However, despite the

gonadotropin treatment, azoospermia was sustained.

- At present, no treatments are available for the lack of sense of smell, mirror movements of the hands, or the unilateral renal agenesis.

Do patients need a life-long hormone replacement?

- Kallmann syndrome usually means a lifelong hormone replacement treatment for male patients, but for females only until the expected time of menopause.
- In about 10–15% of patients, a recovery of their hormonal system may occur, but the reasons are unclear.

Does Kallmann syndrome affect the life expectancy of patients?

- Kallmann syndrome is not associated with decreased life expectancy, but can be accompanied with osteopenia or osteoporosis.

Tips

The reader is advised to read the preceding chapter on hypopituitarism (▶ Chap. 6) and also the chapters dealing with primary hypogonadism, where the end organs (ovaries and testicles) of the hypothalamic-pituitary-gonadal axes are dysfunctioning (Turner syndrome (▶ Chap. 40), primary ovarian insufficiency (▶ Chap. 41), and Klinefelter syndrome (▶ Chap. 42)).

Take-Home Messages

- Kallmann syndrome is an isolated form of hypogonadotropic hypogonadism with hyposmia/anosmia (dysfunction of sense of smell)
- Kallmann syndrome is a rare congenital disease with various inheritance patterns
- The illness can be associated with minor anomalies such as midline facial defects, renal agenesis, short metacarpus, and synkinesia
- Lifetime sexual hormone replacement therapy is indicated for male patients, whereas in women it is proposed until the expected time of menopause.

Suggested Reading

1. Boehm U, Bouloux PM, Dattani MT, de Roux N, Dodé C, Dunkel L, Dwyer AA, Giacobini P, Hardelin JP, Juul A, Maghnie M, Pitteloud N, Prevot V, Raivio T, Tena-Sempere M, Quinton R, Young J. European Consensus Statement on congenital hypogonadotropic hypogonadism—pathogenesis, diagnosis and treatment. Nat Rev Endocrinol. 2015;11:547–64. https://doi.org/10.1038/nrendo.2015.112.
2. Krausz C, Riera-Escamilla A. Monogenic forms of male infertility. Experientia Suppl. 2019;111:341–66. https://doi.org/10.1007/978-3-030-25,905-1_16.
3. Raivio T, Falardeau J, Dwyer A, Quinton R, Hayes FJ, Hughes VA, Cole LW, Pearce SH, Lee H, Boepple P, William F, Crowley WF, Pitteloud N. Reversal of idiopathic hypogonadotropic hypogonadism. N Engl J Med. 2007;357:863–73. https://doi.org/10.1056/NEJMoa066494.
4. Stamou MI. Georgopoulos: Kallmann syndrome: phenotype and genotype of hypogonadotropic hypogonadism. Metabolism. 2018;86:124–34. https://doi.org/10.1016/j.metabol.2017.10.012.

Hypophysitis

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Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_8

Opening

In this chapter, the reader will get acquainted with the clinical features, diagnostic challenges, and management strategies in patients with hypophysitis – an inflammatory disease affecting the pituitary gland.

Definition of the Disease

Hypophysitis is an inflammatory condition of the pituitary gland and its stalk of autoimmune etiology leading to pituitary dysfunction and mass effects. Hypophysitis can occur as a primary condition or secondary to systemic or local lesions, such as Rathke's cleft cyst, craniopharyngioma, or germinoma. Therefore, hypophysitis is a heterogeneous disease.

Primary lymphocytic hypophysitis is caused by an autoimmune reaction directed against the pituitary gland, which becomes pathologically infiltrated by lymphocytes. It is associated with familial or personal history of autoimmune disease. It occurs predominantly in females who are between 30 and 40 years of age. The incidence is estimated to be ~1 in nine million/year. In about 11% of women, it occurs during pregnancy or in the postpartum period.

Xanthogranulomatous hypophysitis (XGH) can present as a separate entity (developing spontaneously) or as a secondary reaction to local process in the sellar region, e.g., following rupture of Rathke's cleft cyst with subsequent inflammation due to the leak of cystic contents or secondary to hemorrhage (apoplexy) of a pituitary adenoma. The typical histopathological findings are cholesterol clefts, hemosiderin deposits, multinucleated giant cells, and small epithelial clusters. Radical surgery is the treatment of choice. Granulomatous (sarcoidosis, Wegener granulomatosis) and necrotizing hypophysitis are rare forms.

Hypophysitis secondary to IgG4-related fibro-inflammatory condition with multiple organs affected and drug-induced hypophysitis (adverse effect of novel monoclonal antibodies targeting immune check points such as cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and programmed cell death protein-1 (PD1) and its ligand (PD-L1)) have renewed interest in pituitary inflammation.

Since hypophysitis is rare, limited experience is available and practice guidance on optimal management is still lacking.

Case Report 1: A 14-Year-Old Adolescent with a Pituitary Lesion

Clinical Signs and Symptoms

A previously healthy 14-year-old adolescent girl presented with a 2-week history of severe headache, blurred vision, and diplopia. She also reported amenorrhea. Her past history was uneventful, except for a mild respiratory viral infection 1 month prior to the onset of headache. She had positive family history for autoimmune disease (mother had Sjogren's syndrome). Physical examination revealed sixth cranial nerve palsy.

Investigation

Initial blood cell count and sedimentation rate were normal. A complete immunological workup, including thyroid auto-antibodies, was negative, except for ANA (antinuclear antibody) positivity (nucleoplasma homogeneous positive 1:640). Serum IgG4 level was normal. Lumbar puncture showed clear cerebrospinal fluid (CSF) without cellular presence (malignant cells or leukocytes), normal protein level, and normal tumor markers such as αFP (alpha

fetoprotein) and βhCG (human choriogonadotropin β) levels. Tests for tuberculosis and sarcoidosis were negative.

A cerebral magnetic resonance imaging (MRI) scan revealed an intrasellar and suprasellar lesion with dural tail and tongue-like extension to the infundibulum and with edematous optic chiasm (Fig. 8.1a–c).

Two weeks after the beginning of the initial symptoms (headache, blurred vision, and diplopia), the patient felt unwell again. She complained of severe tiredness, dizziness, malaise, nausea, and

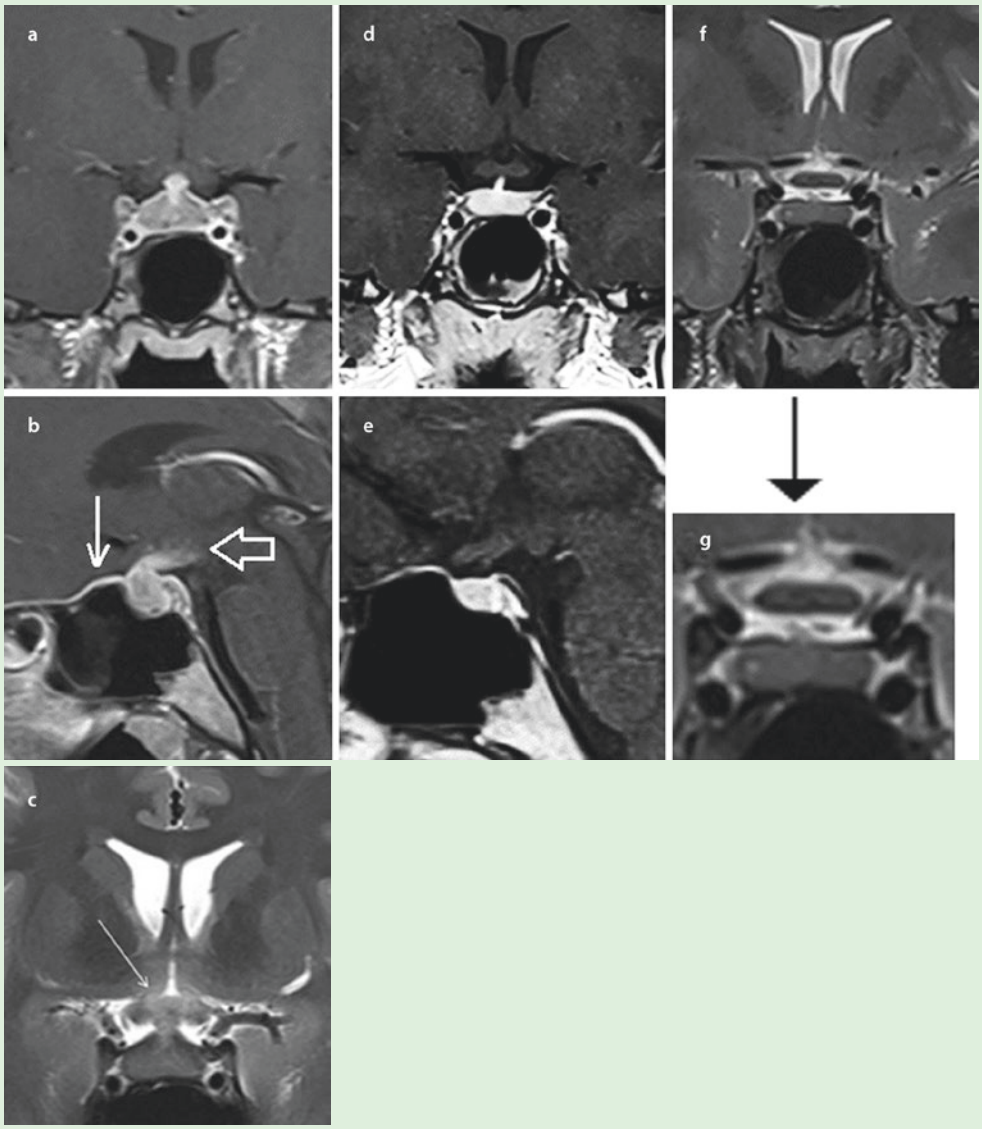

Fig. 8.1 Sellar MRI scan. **a** Coronal T1WI scan at presentation showing symmetrically enlarged pituitary gland with suprasellar extension and thickened pituitary stalk. **b** Sagittal T1WI scan at presentation showing presellar dural tail (arrow) and tongue-like extension to the infundibulum (hollow arrow). **c** Coronal T2WI scan at presentation showing edema of the optic chiasm (arrow). **d** Coronal T1WI scan after 8 weeks of glucocorticoid therapy showing regression of the pituitary mass and normal pituitary stalk. **e** Sagittal T1WI scan after 8 weeks of glucocorticoid therapy. **f, g** Coronal T2WI scan after 8 weeks of glucocorticoid therapy

vomiting. Baseline hormonal evaluation revealed multiple anterior pituitary hormone deficiencies with hyperprolactinemia (Table 8.1). Posterior pituitary function was normal.

The patient was started on replacement doses of oral hydrocortisone and L-thyroxine.

Table 8.1 Results of endocrine testing at baseline and during treatment

Hormone	Baseline	On prednisone			Off prednisone	Reference range
		1 month	2 months	3 months	1 month	
FT4 (pmol/L)	8.8	15.6	19.2	17.8		12–22
TSH (mIU/L)	0.5	1.28	3.33	1.87		0.3–5.5
Cortisol (nmol/L)	221		111	209	425	131–642
FSH (IU/L)	0.5	6.4	4.7	6.7		3.5–12.5
LH (IU/L)	0.1	4.32	2.01	2.79		2.4–12.6
Estradiol (pmol/L)	88	99	128	88		77–921
PRL (mIU/L)	1487	541	715	513		102–496
IGF-1 (ng/ml)	244					208–444

Normal values for FSH, LH, and estradiol for follicular phase

Which of these signs and symptoms could raise the suspicion for hypophysitis?

Headache and visual disturbances due to compression of optic chiasma are the most prevalent presenting symptoms in patients with hypophysitis and are described in up to 50% of cases. Other signs and symptoms which could raise the suspicion for hypophysitis include cranial nerve palsies and polydipsia/polyuria (in patients with infundibulo-neurohypophysitis).

What kind of hormonal alterations can be seen in patients with lymphocytic hypophysitis?

The most common pituitary hormone abnormalities in patients with lymphocytic hypophysitis include ACTH deficiency (in about half of cases), followed by TSH and FSH/LH deficiency (in about 40% of cases), growth hormone deficiency (in up to 30% of cases), and hyperprolactinemia (in 25% of patients). Hyperprolactinemia may be related to stalk compression. A deficiency of the hormone arginine vasopressin (AVP) is presenting hormone abnormality in patients with infundibulo-neurohypophysitis.

What additional investigations would you perform?

Brain ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET-CT) scan is a diagnostic method for distinguishing between benign and malignant lesions. It reflects the degree of glucose utilization by the pathological processes (tumor, inflammation, etc.).^{18}F-FDG PET-CT is important when multisystem disease is suspected such as IgG4-related disease and Langerhans cell histiocytosis to identify the involved organs most suitable for biopsy. In our patient, the

finding of increased glucose metabolism in mesencephalon, proximal pons, and slightly in hypothalamus was interpreted as an inflammation affecting the hypothalamic region and surrounding brain structures only without systemic effects (Fig. 8.2).

What other diseases can be considered in the differential diagnosis of hypophysitis?

Other neoplastic, infiltrative, and inflammatory diseases have to be considered in the differential diagnosis of hypophysitis, such as germinoma, Langerhans cell histiocytosis, and neurosarcoidosis. Other less probable differential diagnoses include pituitary adenomas, Rathke's cleft cyst, physiological hypertrophy of the pituitary in pubertal females, TSH hyperplasia associated with severe primary hypothyroidism, and various sellar and parasellar tumors (e.g., craniopharyngiomas, gliomas, lymphomas, meningiomas, pituicytomas, chordomas, teratomas, dermoids, epidermoid, and sellar metastases).

Is there a role for pituitary biopsy?

Yes, there is a role for pituitary biopsy in order to obtain histopathological verification of the diagnosis, but sometimes it is not feasible because of the patient's condition. Since pituitary biopsy was not obtained, neurosarcoidosis and Langerhans cell histiocytosis remained as differential diagnosis in our patient. Germinoma was excluded on the basis of normal αFP and βhCG levels in serum and CSF. Multidisciplinary team decided to postpone biopsy after a trial with corticosteroid therapy, in case of lack of response to treatment or a relapse of the disease after successful treatment with corticosteroids.

How would you manage this patient?

A short course of high-dose oral glucocorticoids (prednisone 60 mg daily during 2 weeks, then 40 mg daily next 2 weeks, followed by gradual tapering of prednisone dose) was initiated. After 1 month of glucocorticoid therapy, significant improvement of her neurological status occurred with partial recovery of pituitary function (thyroid function recovered with normalization of prolactin level; Table 8.1).

Outcome and Follow-Up

Sellar MRI scan at follow-up (after 8 weeks) showed regression of the pituitary lesion (Fig. 8.1d–g). Along with pituitary mass shrinkage, there was some residual tissue heterogeneity but a thin peripheral dark T2-weighted image (WI) hypointense ring with no enhancement after gadolinium, probably related to some fibrosis. The stalk normalized. The patient did not require thyroid and adrenal replacement therapy 4 months after her hospitalization. She continues to present with secondary amenorrhea, although her gonadotropin levels suggest recovery of the gonadotropic axis.

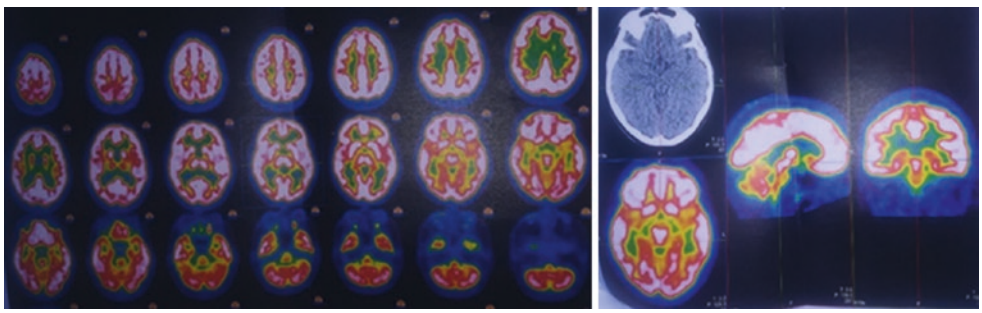

Fig. 8.2 Brain ^{18}F-FDG PET/CT scan shows increased glucose metabolism in mesencephalon, proximal pons, and hypothalamus

Learning Points

- This case highlights the rare cause of hypopituitarism with severe neurological impairments due to a pituitary lesion with a differential diagnosis of lymphocytic hypophysitis in the pediatric age group.
- The diagnosis in our patient was based on hormonal findings and the radiological aspect of the lesion (MRI) despite the lack of histopathology.
- Despite diagnostic uncertainty, high-dose glucocorticoid treatment in our patient was successful leading to clinical and radiological improvement.
- The favorable evolution of our patient with near-normal hormone recovery on corticosteroid treatment is in favor of lymphocytic hypophysitis, although the final diagnosis remains unclear.

Case Report 2: A 42-Year-Old Woman with Relapsing, Corticosteroid Non-responsive Lymphocytic Hypophysitis

Clinical Signs and Symptoms

A 42-year-old woman presented with a 2-year history of severe headache, double vision, and amenorrhea. According to her clinical and radiological findings (MRI scans), she was diagnosed with lymphocytic hypophysitis and treated with corticosteroids (prednisone 20 mg) for 2 years while living abroad. At presentation in our hospital she had severe headache, dizziness with severe signs of iatrogenic Cushing's syndrome, and diplopia due to right sixth cranial nerve palsy. She also had complete obstruction of the left internal carotid artery, secondary to propagation of inflammation to the cavernous sinus and arteritis (primary autoimmune vasculitis was excluded). Prednisone therapy was tapered and stopped. The patient had secondary hypocorticism (adrenal insufficiency) (was replaced with hydrocortisone 20 mg/day) and mild hyperprolactinemia (Table 8.2). Her MRI scan showed a large pituitary mass with right parasellar propagation (Fig. 8.3a).

Table 8.2 Hormonal analysis before operation and during the follow-up period

Hormone	Before OP	3 months after OP	1 year after OP	2 years after OP, 1 year after SRS	4 years after OP, 3 years after SRS	Reference range
Therapy	**PR off**	**PR 20 mg AZ 50 mg**	**PR 20 mg AZ 50 mg**	**PR 10 mg AZ 50 mg**	**PR 7.5 mg AZ off**	
FT4 (ng/L)	11.7	11.2	11.6	8.9	5.8	7–18
TSH (mIU/L)	1.14	0.31	4.7	2.0	2.8	0.3–5.5
Cortisol (nmol/L)	38.9		156.1	56.9	22	131–642
FSH (IU/L)	3.4	14.9	5.8	14.7	6.5	2.5–15
LH (IU/L)	2.7	3.5	5.7	5.5	1.5	4–20
PRL (mIU/L)	1003	905	1234	648	418	
IGF-1 (ng/ml)	177		104	98.5	119	101–267

Reproduced with permission and modifications from Pekic et al. [11]
Abbreviations: *OP* operation, *SRS* stereotactic radiosurgery, *PR* prednisone, *AZ* azathioprine
Normal values for FSH, LH, and estradiol for follicular phase

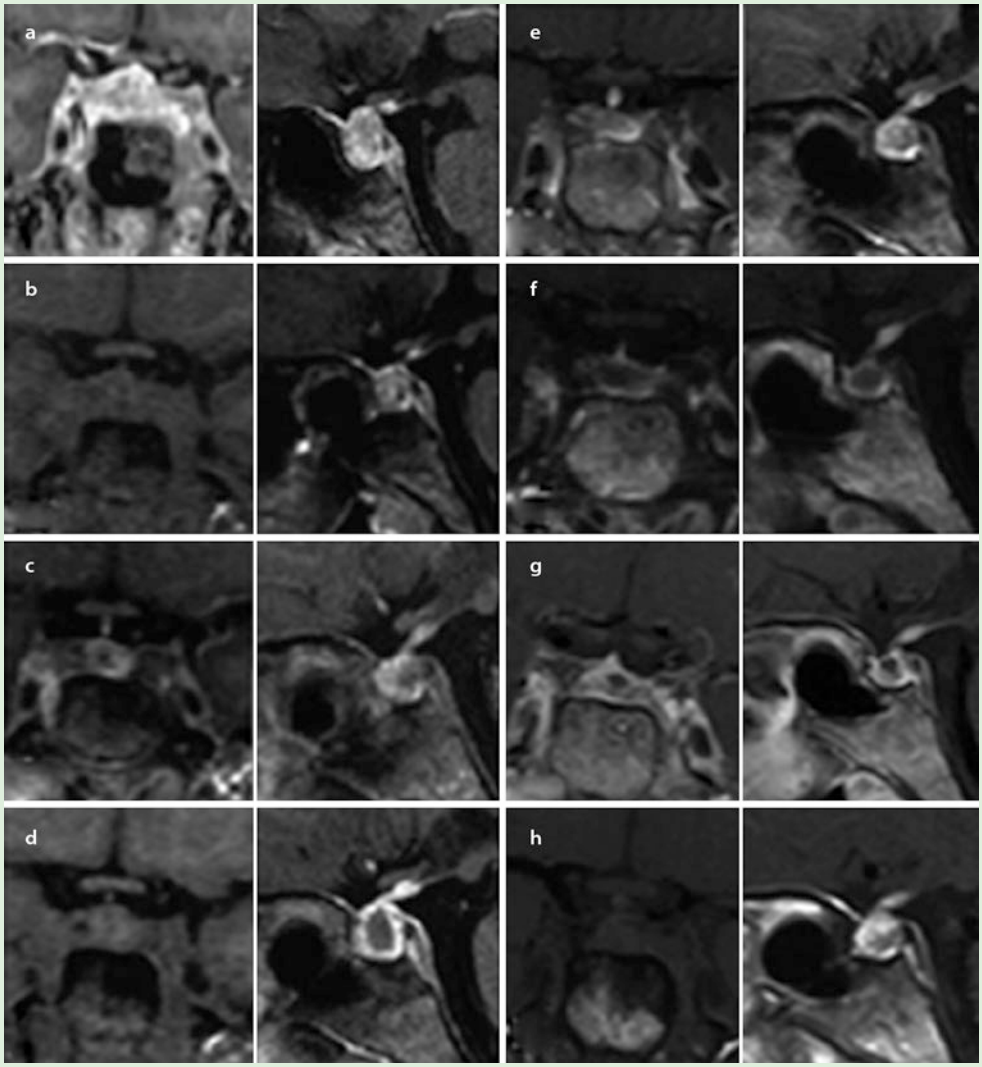

Fig. 8.3 Magnetic resonance imaging of the sellar region, coronal (left) and sagittal (right): **a** before the transsphenoidal decompression; **b** 2 months after the operation; **c** 3 months after the operation; **d** 1 year after the operation when the patient was referred for stereotactic radiosurgery (SRS); **e** 2 years after the operation and 1 year after SRS; **f** 3 years after the operation and 2 years after SRS; **g** 3.5 years after the operation and 26 months after SRS; **h** 4.5 years after the operation and 40 months after SRS. (Reproduced with permission from Pekic et al. [11])

How would you treat this patient in whom corticosteroid therapy was ineffective?

(a) Pituitary Surgery

The patient was referred to the neurosurgeon for decompression and biopsy. Histopathologic analysis revealed infiltration of the pituitary with lymphocytes, plasma cells, rare eosinophils, and macrophages (Fig. 8.4a). Most of the lymphocytes were of T-cell origin (CD3+) (Fig. 8.4b). Two months after the surgery, MRI scan showed a normal pituitary gland (Fig. 8.3b), and

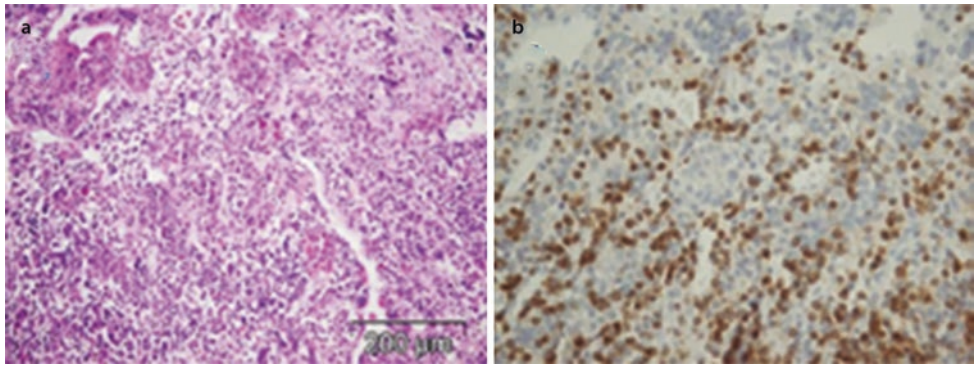

Fig. 8.4 **a** Fragment of anterior pituitary gland with residual islands of preserved acini, separated by dense inflammatory infiltration, composed predominantly of lymphocytes (hematoxylin and eosin, ×200). **b** Most lymphocytes are of T-cell origin (immunohistochemistry, CD3+, ×400). (Reproduced with permission from Pekic et al. [11])

the patient was symptom free. Three months after surgery, the patient suffered from severe headache and diplopia again and MRI scan showed enlarged pituitary gland (Fig. 8.3c).

Surgery is indicated when there is significant mass effect and to exclude the diagnosis of tumor. Acute phase of hypophysitis with severe headache, cranial nerve palsies, visual field defects are indications for surgical decompression. It quickly controls the mass effect, headache, diplopia, and visual impairment, but the rate of recurrence after surgery is reported to be up to 25% and some patients may develop hypopituitarism and diabetes insipidus. Surgery also provides a histological specimen, and histological diagnosis helps with guidance for management.

Histological assessment is important for confirmation and classification of hypophysitis. Histology identifies inflammatory cells (CD3-T cells, CD20-B cells, CD138-plasma cells, CD68-macrophages), histiocytes, granulomas, and xanthomas.

(b) Other Immunosuppressive Therapies

Hypophysitis (headache and diplopia) reappeared 6 months after surgery. The patient was treated with stress doses of corticosteroids (methylprednisolone 120 mg intravenous for 3 days, switched to prednisone 80 mg orally, with gradual tapering of the prednisone dose). When the dose of prednisone was reduced to 10 mg daily, her headache and diplopia reappeared. We added azathioprine (50 mg daily) to prednisone (20 mg daily).

In cases with progressive, recurrent disease or resistance, other immunosuppressive agents or radiotherapy has been considered. Azathioprine is the most commonly used immunosuppressive agent, as well as methotrexate, mycophenolate, and biological therapy with monoclonal antibodies (e.g., rituximab and infliximab).

(c) Gamma Knife Stereotactic Radiosurgery

Six months after combination therapy, our patient was referred to Gamma Knife stereotactic radiosurgery (SRS). The whole intrasellar area (1.5 ml in volume, Fig. 8.3d) was shot with three 8-mm collimators. The prescribed dose was 15 Gy to the margin (50%). Azathioprine was stopped after 26 months of therapy, while prednisone continued at a dose of 10 mg daily. Two years after stereotactic radiosurgery, the dose of prednisone was reduced to 7.5 mg daily and pituitary MRI scan showed no residual pituitary lesion (Fig. 8.3e–h). During 3 years

of follow-up, she developed secondary hypogonadism and hypothyroidism and was replaced with L-thyroxine (Table 8.2). Her prolactin level normalized.

Which patients are candidates for stereotactic radiosurgery?

There are only few case reports on the use of SRS for the treatment of hypophysitis. Stereotactic radiosurgery (SRS) is a radiation therapy modality that allows precise delivery of high dose of irradiation to well-defined small targets using single fraction or multi-fractions SRS (two to five fractions). Delivery systems used for SRS include the cobalt-50 system Gamma Knife, the CyberKnife Robotic Radiosurgery System, or a modified conventional radiotherapy machine (LINAC). Radiation-induced hypopituitarism is the most frequent side effect of SRS occurring within the first 5 years following radiosurgery.

Case Report 3: A Patient with Acromegaly with a New Cystic Sellar Lesion 10 Years After Initial Diagnosis

Patient History

A 37-year-old female presented in the year 2005 with amenorrhea and galactorrhoea, 2 years after her second delivery. She started noticing changes in appearance suggestive of acromegaly, accompanied by headache, edema, and elevated blood pressure 3 years before the diagnosis of acromegaly.

Investigation and Treatment of Acromegaly

Acromegaly was diagnosed based on clinical features (▶ Chap. 3), elevated IGF-1 (723 ng/ml (2.5 ULN)), and growth hormone (GH) with hyperprolactinemia (PRL levels 5500 mIU/l). A mixed GH + PRL secreting pituitary tumor was diagnosed. MRI scan disclosed a pituitary tumor 20 mm in diameter with infra and left parasellar extension.

Primary medical treatment was offered with dopamine agonist (cabergoline) plus long-acting somatostatin analogue (SSA) resulting in normalization of menstrual cycles, loss of galactorrhea, normalization of PRL levels, with significant reduction of IGF-1 (1.2 ULN) and GH levels (Fig. 8.5). It also reduced tumor mass by half (11 mm) (Fig. 8.6).

Our patient was well controlled both clinically and biochemically and she refused pituitary surgery.

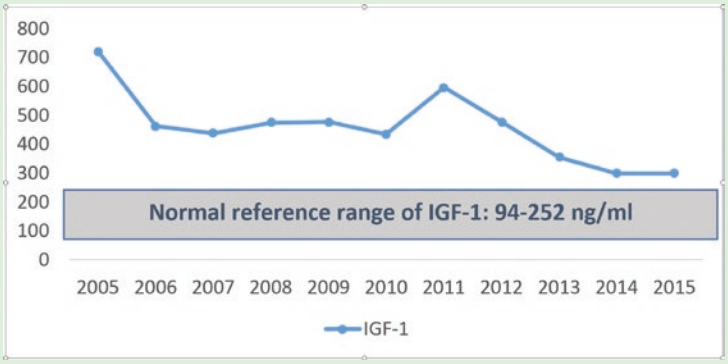

Fig. 8.5 IGF-1 values during follow-up of primary medical treatment for acromegaly with dopamine agonist and somatostatin analogue before pituitary surgery in 2015

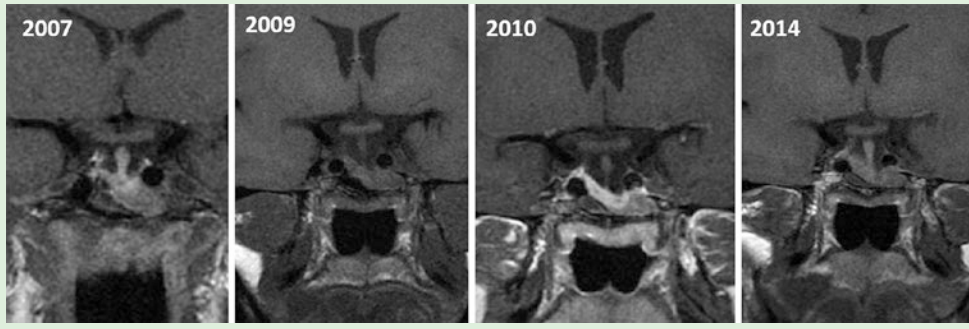

Fig. 8.6 Pituitary MRI TW1 coronal sections with contrast enhancement during follow-up of medical treatment for acromegaly (monthly somatostatin analogue and dopamine agonist) in 2007, 2009, 2010, and 2014. Small tumor remnant is reported just below the left cavernous sinus

Follow-Up

Ten years after the initial diagnosis of acromegaly, our patient experienced new and severe type of headache. Pituitary MRI revealed a cystic mass in the sella, with different localization and MRI characteristics compared to previous adenoma (Fig. 8.7). This round cystic lesion showed strong peripheral contrast enhancement.

Postoperative Follow-Up: After surgery, IGF-1 levels were still mildly elevated (454 ng/ml (1.8 ULN)) and SSA was reintroduced leading to complete normalization of IGF-1 and GH levels. As a consequence of pituitary surgery, the patient developed central hypothyroidism and diabetes insipidus. She was replaced with L-thyroxine and desmopressin.

Xanthomatous hypophysitis is very rare (3%). There is a female preponderance (female to male ratio 3:1), with mean age of presentation in the fourth decade of life. It is usually a round cystic lesion with firm fibrous capsule and liquid yellow content. Histopathology confirmed the diagnosis of xanthomatous hypophysitis with lipid-rich macrophages (foamy histiocytes), plasma cells, and small lymphocytes without granuloma formation. Fibrosis of the capsule was prominent.

Secondary etiology is more common and usually associated with the preexisting pituitary lesions (adenoma, Rathke's cleft cyst, craniopharyngioma). Subclinical pituitary apoplexy may trigger inflammatory response to necrotic tissue. Nearly 32% of hypophysitis present on MRI as cystic lesions.

We have presented an unusual case of xanthomatous hypophysitis developing subacutely with new type of headache after a decade of successful medical treatment of acromegaly. A new cystic pituitary lesion was detected on MRI, and after pituitary surgery xanthomatous hypophysitis was confirmed.

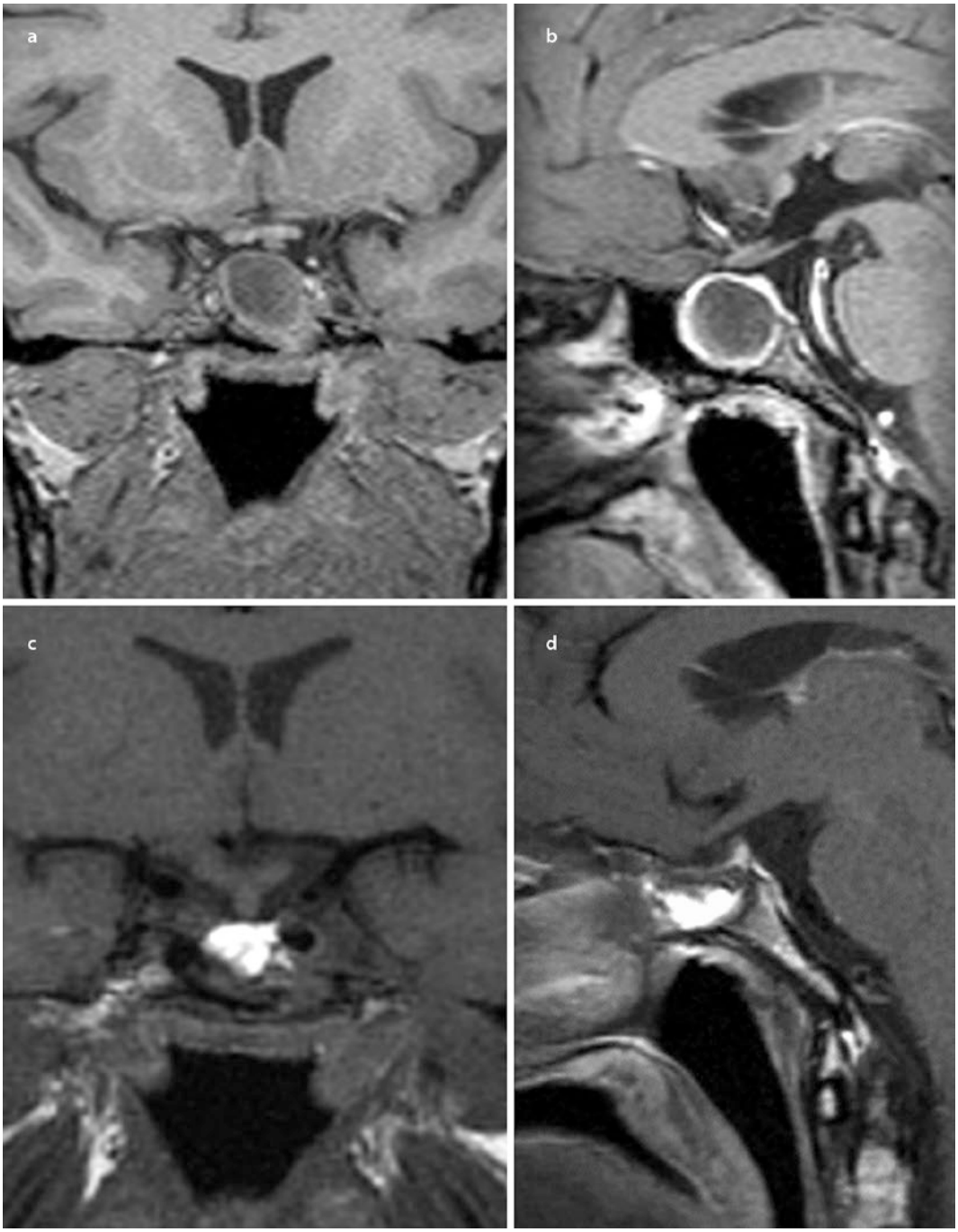

Fig. 8.7 Pituitary MRI TW1 with contrast coronal **a**, **c** and sagittal sections **b**, **d** before surgery for the cystic lesion in 2015 **a**, **b** and after pituitary surgery in 2015 **c**, **d** showing that the lesion was completely resected

What is the next step in diagnosis and management?

Surgery was the next step in the management of our patient. The cystic lesion was removed by pituitary transsphenoidal surgery.

Intraoperative findings revealed the well-defined round firm cystic brownish formation, very tightly attached to the pituitary, filled with yellow liquid, which was completely resected. No pituitary adenoma was found.

Histopathology report was consistent with xanthomatous hypophysitis. Lipid-rich macrophages were dominant to some plasma cells and small lymphocytes in the inflammatory infiltrate (Fig. 8.8). No tumor tissue of pituitary adenoma was identified, only normal pituitary acini.

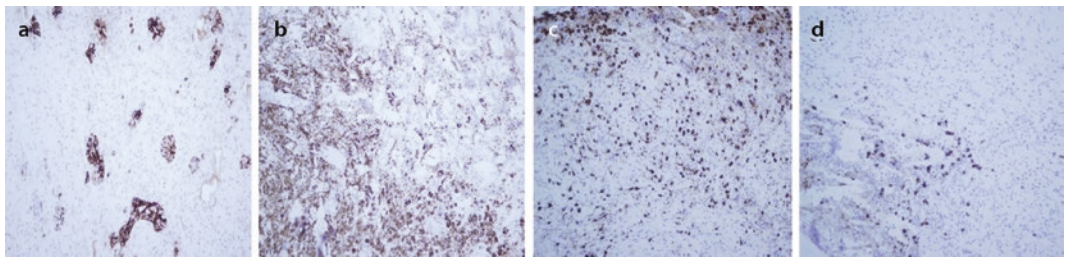

Fig. 8.8 **a** Immunohistochemistry showing pancytokeratin AE1/AE3 positive acini of anterior pituitary separated by inflammatory cells. **b** Inflammatory infiltrate is predominantly composed of lipid-rich macrophages (CD68), **c** T lymphocytes CD3 positive, and **d** rare B lymphocytes CD20 positive

8

Learning Points

- Xanthomatous hypophysitis is rare and usually of secondary etiology, more common in middle-aged women.
- It can present with mass effect symptoms (e.g., headache and visual disturbances) and/or pituitary dysfunction (e.g., hyperprolactinemia, hypopituitarism, and diabetes insipidus).
- Surgery may relieve compressive symptoms, but pituitary function may be affected and should be followed up.
- MRI features of cystic pituitary lesion, with rim contrast enhancement, is challenging with differential diagnosis of hypophysitis from a sellar abscess.
- Histopathology confirmed xanthomatous hypophysitis by demonstrating large number of lipid-rich macrophages (foamy histiocytes) without granuloma formation and some plasma cells and small lymphocytes. Fibrosis may also be prominent, as well as liquid content of the cystic lesions rich in cholesterol crystals.

Case Report 4: A 12- Year-Old Girl with Diabetes Insipidus and Pituitary Stalk Thickening

Clinical Signs and Symptoms

A 12-year-old girl was referred to us for further endocrine evaluation and management. At the age of 8 years, she was diagnosed with central diabetes insipidus thought to be consequence of traumatic brain injury. She had serial yearly MRI scans at the request of pediatric endocrinologist. At the age of 12 years, MRI showed a sellar and suprasellar lesion markedly enhanced after gadolinium injection, with thickening of the pituitary stalk (Fig. 8.9).

On examination, she was of normal height and weight and no pubertal development was observed.

Investigations

Routine biochemistry was normal. Serum tumor markers αFP and βHCG were negative.

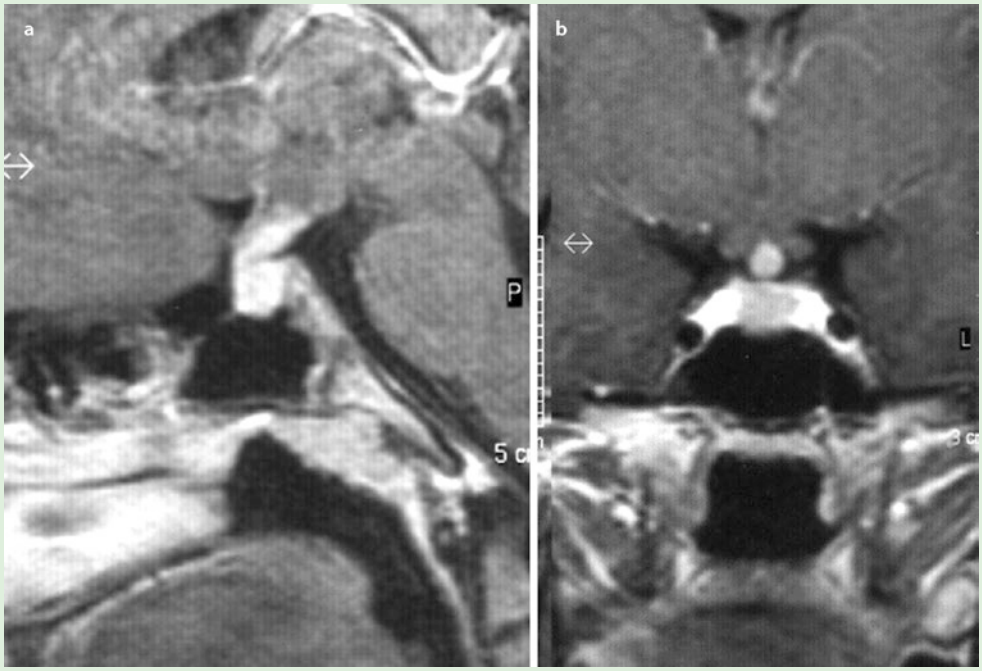

Fig. 8.9 Pituitary MRI TW1 sagittal **a** and coronal sections **b** showed sellar and suprasellar lesion markedly enhanced after gadolinium injection, with thickening of the pituitary stalk

Which pituitary disorder do you suspect and why?

The differential diagnosis is broad (sarcoidosis, histiocytosis, tumor, lymphoma, infection, etc.), but in our patient, germinoma should be suspected based on the fact that the most common cause of pituitary stalk thickening and diabetes insipidus in pediatric age is neoplastic process.

She was referred to neurosurgery for transcranial pituitary biopsy. Histopathology report revealed lymphocytic hypophysitis. In addition to diabetes insipidus, she developed anterior hypopituitarism. Based on the massive lymphocytic infiltration of the pituitary stalk-infundibulum (thickening) and diabetes insipidus in a young girl, we suspected a neoplastic process (germinoma).

How would you treat this patient?

Our patient was treated with radiation therapy. She received a dose of 30 Gy. Six months after radiation therapy, MRI showed resolution of hypophysitis. Hypopituitarism and diabetes insipidus persisted. At present, she is 28 years old, is in remission for germinoma, and is seeking fertility.

Learning Points

- The case shows the difficulties in establishing the correct diagnosis of a lesion in the sellar/suprasellar (stalk thickening) region.
- Pituitary stalk thickening in pediatric age is mostly attributed to neoplastic process (germinoma).
- Hormonal dysfunctions (diabetes insipidus) precede MRI findings.
- This case report emphasizes the role of serial MRI scanning in young patients diagnosed with central diabetes insipidus (follow-up at 3- to 6-month intervals first year and then yearly).
- Lymphocytic hypophysitis and germinoma share similar clinical presentation and radiological features.
- Germinomas are highly immunogenic tumors which present with marked diffuse lymphocytic infiltration.

Case Report 5: Iatrogenic Hypophysitis in a Cancer Patient Treated with Immune Checkpoint Inhibitors

A 57-year-old man visits the hospital for his fourth injection of immunotherapy for a metastatic melanoma (splenic and pulmonary metastases). He should receive ipilimumab (anti-CTLA-4) 3 mg/kg, but he reported headache, despite analgesic treatment, asthenia, nausea, and dizziness. He denied increased thirst or increased urination. At physical examination, he had a blood pressure of 85/45 mmHg and had difficulty with walking because of dizziness and muscle aches. Biochemical evaluation showed borderline hyponatremia (135 mmol/L), with no inflammatory syndrome. The ipilimumab injection was canceled as the patient was vomiting.

What is the diagnosis and how would you manage this patient?

In the setting of clinical symptoms, hypotension and borderline hyponatremia, ACTH deficiency and hypophysitis were suspected. Hormonal evaluation was assessed and pituitary MRI was performed. The patient immediately received intravenous hydrocortisone (100 mg) treatment without waiting for cortisol values or imaging results. Hormonal results on administration showed low cortisol level (25 nmol/L) with low ACTH (5 pg/ml); and low TSH (0.1 mIU/l) with low fT4 (6 pmol/L) and with low prolactin level (0.5 ng/ml). Gonadotropin axis showed low testosterone (500 pg/ml) with low LH and FSH (0.1 IU/L and 0.2 UI/L, respectively). The patient reported low libido and erectile dysfunction, but this could also be attributed to the oncologic disease.

The pituitary MRI scan showed a moderate enlargement of the pituitary gland, with heterogeneous contrast enhancement of this convex pituitary (Fig. 8.10a, b).

Rapidly after intravenous hydrocortisone, the patient felt better with normalization of blood pressure. As symptoms such as

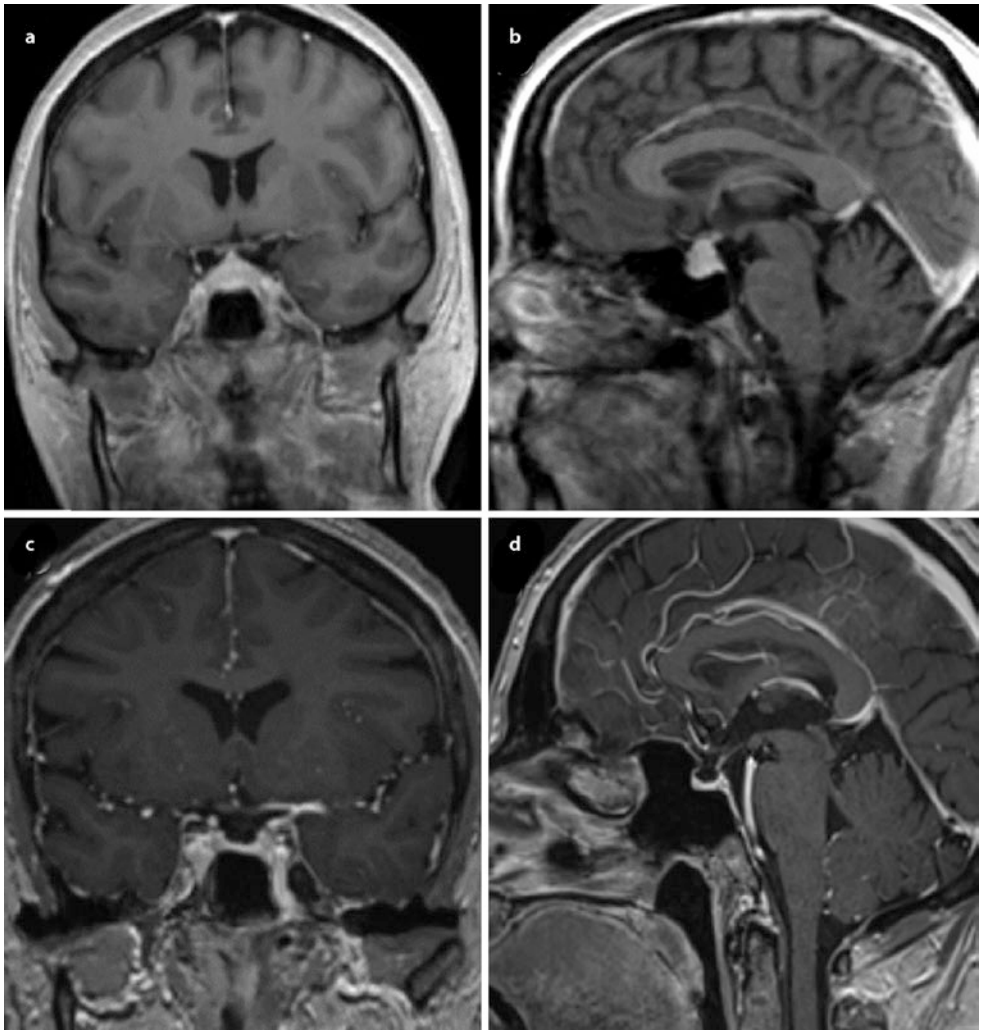

Fig. 8.10 Pituitary MRI of immunotherapy-induced hypophysitis: **a** day 3, coronal plane post-gadolinium T1-weighted images; **b** day 3, sagittal plane of gadolinium T1-weighted images; **c** 3 months of follow-up, coronal plane post-gadolinium T1-weighted images; **d** 3 months of follow-up, sagittal plane of gadolinium T1-weighted images

nausea and vomiting quickly resolved, the patient was immediately switched to oral replacement doses of hydrocortisone. High-dose glucocorticoids were not given as the degree of pituitary enlargement was mild to moderate and there was no optic chiasm compression.

Immunotherapy treatment was continued after few days of delay in order to allow the patient to recover from his weakness. He remained on daily hydrocortisone 30 mg treatment (3 intakes of 10 mg per day) and received hydrocortisone education for adaptation to stress.

Testing for recovery of pituitary function was performed every 3 weeks and results showed a rapid increase in testosterone and prolactin levels, with complete normalization after 2 months. Thyrotropin axis was stable and spontaneously improved at 6 weeks evaluation. However, ACTH deficiency did not recover. Low baseline cortisol levels (<10 nmol/L) and very low ACTH (<3 pg/mL) persisted

when evaluated at 3 months and after 3 years interval.

A pituitary MRI was performed to check the pituitary evolution (and definitively rule out, in this context, the differential diagnosis of pituitary metastasis). It showed a major decrease of pituitary volume, with an aspect of empty sella turcica (Fig. 8.10c, d). At the end of follow-up, 3 years later, pituitary MRI remained unchanged from the 3-month assessment.

What should we learn from this case report? Key points About immunotherapy-induced hypophysitis

- Hypophysitis is a common adverse event in patients receiving immunotherapy, especially CTLA-4 inhibitor (ipilimumab) alone or in combination with PD-1 inhibitors (pembrolizumab or nivolumab) or PD-L1 inhibitors (atezolizumab and durvalumab).
- The most common presenting symptoms are headache, fatigue, asthenia, nausea, and hypotension. Gonadotropin, thyrotropin, and corticotropin deficiencies are common while diabetes insipidus and visual disturbances are rare.
- MRI usually shows mild to moderate enlargement of the pituitary gland in acute phase, and with resolution of hypophysitis, reduced pituitary volume or empty sella is observed. This evolution allows to rule out the differential diagnosis of brain metastases.
- In case of corticotropin deficiency, glucocorticoid treatment is an emergency. Systemic high-dose glucocorticoid treatment is not necessary unless the patient is experiencing compressive symptoms (impaired vision due to mass effect on optic chiasm).
- After a short delay until the patient is clinically stable, continuation of immunotherapy is recommended.
- Testing for recovery of pituitary function can be performed at 3–6 months interval, but corticotropin deficiency remains in most cases and requires treatment with replacement doses of glucocorticoids.

Tips

The reader is advised to read the following chapters: Hypopituitarism (▶ Chap. 6), Acromegaly (▶ Chap. 2), and Non-functioning pituitary adenoma (▶ Chap. 4).

Take Home Messages

- Hypophysitis is a rare primary (idiopathic) or secondary inflammation of the pituitary gland, affecting adenohypophysis, infundibulo-neurohypophysis, or both (panhypophysitis).
- Hypophysitis can present with mass effect symptoms (headache, visual disturbances, cranial nerve palsies) and/or pituitary dysfunction (hypopituitarism, hyperprolactinemia, diabetes insipidus).
- The diagnosis of hypophysitis is based on clinical, hormonal, and radiological (MRI) data.
- Magnetic resonance imaging is important in differential diagnosis of hypophysitis from other neoplastic, infiltrative, or inflammatory diseases.
- Biopsy and histopathology confirm the diagnosis and type of hypophysitis.
- Glucocorticoids are drugs of choice for patients with severe compressive signs and symptoms.
- Surgery may relieve compressive symptoms in patients who do not respond to glucocorticoids.

Acknowledgments This study was supported by a grant from the Ministry of Science of Republic of Serbia (Project 175033).

Suggested Reading

1. Albarel F, Castinetti F, Brue T. Management of endocrine disease: immune check point inhibitors-induced hypophysitis. Eur J Endocrinol. 2019;181(3):R107–18. https://doi.org/10.1530/EJE-19-0169.
2. Castinetti F, Albarel F, Archambeaud F, Bertherat J, Bouillet B, Buffier P, Briet C, Cariou B, Caron P, Chabre O, Chanson P, Cortet C, Do Cao C, Drui D, Haissaguerre M, Hescot S, Illouz F, Kuhn E, Lahlou N, Merlen E, Raverot V, Smati S, Verges B, Borson-Chazot F. French Endocrine Society Guidance on endocrine side effects of immunotherapy. Endocr Relat Cancer. 2019;26(2):G1–G18. https://doi.org/10.1530/ERC-18-0320.
3. Gutenberg A, Bell JJ, Lupi I, Tzou SC, Landek-Salgado MA, Kimura H, Su J, Karaviti LP, Salvatori R, Caturegli P. Pituitary and systemic autoimmunity in a case of intrasellar germinoma. Pituitary. 2011;14(4):388–94. https://doi.org/10.1007/s11102-009-0187-x.
4. Honegger J, Buchfelder M, Schlaffer S, Droste M, Werner S, Strasburger C, Störmann S, Schopohl J, Kacheva S, Deutschbein T, Stalla G, Flitsch J, Milian M, Petersenn S, Elbelt U, Pituitary Working Group of the German Society of Endocrinology. Treatment of primary hypophysitis in Germany. J Clin Endocrinol Metab. 2015;100(9):3460–9. https://doi.org/10.1210/jc.2015-2146.
5. Honegger J, Schlaffer S, Menzel C, Droste M, Werner S, Elbelt U, Strasburger C, Störmann S, Küppers A, Streetz-van der Werf C, Deutschbein T, Stieg M, Rotermund R, Milian M, Petersenn S, Pituitary Working Group of the German Society of Endocrinology. Diagnosis of primary hypophysitis in Germany. J Clin Endocrinol Metab. 2015;100(10):3841–9. https://doi.org/10.1210/jc.2015-2152.
6. Kleinschmidt-DeMasters BK, Lillehei KO, Hankinson TC. Review of xanthomatous lesions of the sella. Brain Pathol. 2017;27(3):377–95. https://doi.org/10.1111/bpa.12498.
7. Li G, ZHang C, Sun Y, Mu Q, Huang H. Xanthogranulomatous pituitary adenoma: a case report and literature review. Mol Clin Oncol. 2018; 8(3):445–8. https://doi.org/10.3892/mco.2018.1547.
8. Nagi S. Primary hypophysitis. In: Bonneville JF, Bonneville F, Cattin F, Nagi S, editors. MRI of the pituitary gland. Cham: Springer; 2016. p. 283–91.
9. Nakata Y, Sato N, Masumoto T, Mori H, Akai H, Nobusawa H, Adachi Y, Oba H, Ohtomo K. Parasellar T2 dark sign on MR imaging in patients with lymphocytic hypophysitis. Am J Neuroradiol. 2010;31(10):1944–50. https://doi.org/10.3174/ajnr.A2201.
10. Nishioka H, Shibuya M, Ohtsuka K, Ikeda Y, Haraoka J. Endocrinological and MRI features of pituitary adenomas with marked xanthogranulomatous reaction. Neuroradiology. 2010;52(11):997–1002. https://doi.org/10.1007/s00234-010-0675-8.
11. Pekic S, Bogosavljevic V, Peker S, Doknic M, Miljic D, Stojanovic M, Skender Gazibara M, Manojlovic Gacic E, Popovic V. Lymphocytic hypophysitis successfully treated with stereotactic radiosurgery: case report and review of the literature. J Neurol Surg A Cent Eur Neurosurg. 2018;79(1):77–85. https://doi.org/10.1055/s-0037-1604079.
12. Prete A, Salvatori R. Hypophysitis. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, Dungan K, Grossman A, Hershman JM, Kaltsas G, Koch C, Kopp P, Korbonits M, McLachlan R, Morley JE, New M, Perreault L, Purnell J, Rebar R, Singer F, Trence DL, Vinik A, Wilson DP, editors. Endotext [Internet]. South Dartmouth: MDText.com, Inc.; 2000. -.2018 Aug 15.
13. Ved R, Logier N, Leach P, Davies JS, Hayhurst C. Pituitary xanthogranulomas: clinical features, radiological appearance and post-operative outcomes. Pituitary. 2018;21(3):256–65. https://doi.org/10.1007/s11102-017-0859-x.
14. Zhou X, Zhu H, Yao Y, Lian X, Feng F, Wang L, Liu S, Deng K, You H, Yang H, Lu L. Etiological spectrum and pattern of change in pituitary stalk thickening: experience in 321 patients. J Clin Endocrinol Metab. 2019;104(8):3419–27. https://doi.org/10.1210/jc.2018-02297.

Diabetes Insipidus

Eleonora Seelig and Jonas Rutishauser

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_9

Opening

This chapter will discuss basic aspects of fluid homeostasis, focusing on the clinical features and differential diagnosis of diabetes insipidus.

Definition of the Disease

The term diabetes insipidus (DI, "tasteless water flow") refers to the production of large amounts of diluted urine. Defects in the antidiuretic mechanism cause water diuresis in DI, as opposed to the solute diuresis seen, e.g., in uncontrolled diabetes mellitus ("sweet water flow").

Case Presentation

A 57-year-old male patient presented with a history of several years with increased thirst and production of massive amounts of urine, presently measured to be 12 liters in 24 hours. He needed to void and drink every 1–2 hours, causing fragmentation of his sleep and consequent exhaustion. Six years earlier, type 2 diabetes mellitus had been diagnosed. The patient was on treatment with metformin, dapagliflozin, insulin degludec, dulaglutide, aspirin, and lisinopril. It had been suggested to him that his symptoms probably originated from his diabetes mellitus and the treatment with dapagliflozin, an inhibitor of the renal sodium-glucose cotransporter (SGLT) 2, which causes glucosuria and slight volume depletion and can consequently lead to increased thirst. He consulted his family physician, who ordered a magnetic resonance tomography of the hypothalamic-pituitary region. No suprasellar mass was seen, but a thickened pituitary stalk and an abnormal appearance of the posterior pituitary were noted, with a lack of the characteristic neurohypophyseal "bright spot." The patient's glycated hemoglobin was 7.3%, a random serum sodium value was 142 mmol/L (normal, 135–145), and, as expected, glucosuria was present in urinalysis.

The patient was asked to refrain from drinking overnight. On the following morning, after 13 hours of thirsting, serum sodium was 144 mmol/L, glucose 11.6 mmol/L (normal below 5.5), serum osmolality 309 mOsm/kg, and spot urine osmolality 349 mOsm/kg (normal, above ~2.5-fold serum osmolality). The concomitant serum copeptin concentration was 1.8 pM.

A diagnosis of pituitary diabetes insipidus was made. Although the current 24-hour urine production was high (114 ml/kg), it could not be concluded with certainty whether a partial form was present, which was suggested by the urine osmolality slightly exceeding that in the serum, because the interpretation of the relevant values was hampered by the hyperglycemia and iatrogenic glucosuria, respectively.

The patient was started on 10 μg of the synthetic vasopressin analog desmopressin intranasally. He reported an immediate relief of his symptoms, a reduction of the 24-hour urine quantity to 3–4 liters, and a complete cessation of his nocturia. Regarding the alteration of the pituitary abnormality on magnetic resonance imaging (MRI), the differential diagnosis included lymphocytic infundibuloneurohypophysitis, sarcoidosis, neoplastic disease, or a congenital anomaly. A conservative wait-and-see strategy was advised. 8 months later, the patient died unexpectedly while at work.

What are the signs and symptoms of DI?

In untreated DI, the production of large amounts of urine, polyuria, is the main sign, and excessive thirst, polydipsia, is the cardinal symptom (hence the term "polyuria-polydipsia syndrome"). As seen in our case description, patients typically void often also during the night, leading to fragmented sleep and daytime sleepiness. It is important to realize that an intact thirst mechanism is necessary to maintain fluid equilibrium. Thus, in some rare instances where DI results from damage also affecting the hypothalamic "thirst center," such as postoperative states after removal of midline lesions, patients may not sense thirst (adipsia) and are in danger of rapid, potentially fatal dehydration. Chronic dehydration in children with congenital DI results in cognitive deficits and/or failure to thrive. While DI per se is not dangerous as long as there is unrestricted access to fluids, insufficiently controlled polyuria over prolonged periods of time may result in dilation of the descending urinary tract. This can cause vesicoureteral reflux, facilitating recurrent urinary tract infections.

Which other diseases may mimic DI?

As patients may not be aware of the distinction between polyuria and pollakisuria (frequent small voids), the presence of urinary tract infection should be evaluated by medical history and urinalysis. Glucosuria causing solute diuresis in uncontrolled diabetes mellitus should always be sought. As evidenced by our case description, glucosuria is induced by SGLT-2 inhibitors, which can complicate the interpretation of urinary volume and osmolality values. Solute diuresis may also be caused by the excretion of electrolytes, e.g., after administration of large quantities of intravenous saline, by mannitol, or by urea.

What causes DI?

The antidiuretic hormone arginine vasopressin (AVP) regulates the reabsorption of free water in the kidney. It is synthesized as a prohormone in specialized cells of the supraoptic and paraventricular nuclei of the hypothalamus (Fig. 9.1). Pro-AVP is sorted into neurosecretory granules and transported along axons extending to the posterior pituitary, where the granules are stored in the cytoplasm. During transport, the prohormone is processed to the AVP nonapeptide, the carrier protein neurophysin II (NPII), and a C-terminal glycopeptide called copeptin (Fig. 9.2). The main physiological stimuli for granule fusion with the plasma membrane and the cosecretion of AVP, NPII, and copeptin into the systemic circulation are hyperosmolality and hypovolemia. Unspecific stimuli include pain, situations of stress (e.g., acute illness or an operation), or nausea. AVP exerts its antidiuretic effect by binding to the renal type 2 receptor (arginine vasopressin receptor 2, AVPR2), which is expressed at the basolateral membrane of collecting duct cells. AVP binding activates a signal cascade resulting in the insertion of aquaporin-2 "water channel" proteins into the apical cell membrane, allowing the influx of H_2O molecules from the luminal side into the cells and on to the interstitial space

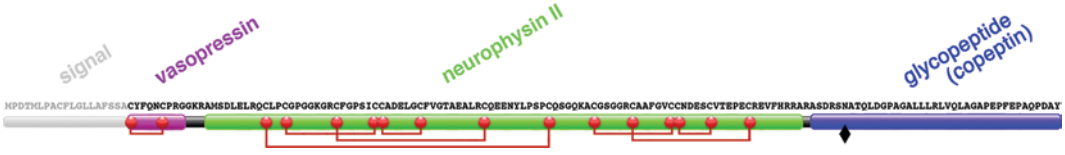

Fig. 9.1 Schematic representation of the vasopressin precursor hormone. Amino acid (aa) residues are indicated with the single letter code. The preprohormone consists of the signal peptide (21 aa; gray), the nonapeptide vasopressin (pink), a 93-aa carrier protein, neurophysin II (green), and the C-terminal glycopeptide of 39 aa (blue). Red dots represent cysteine residues, red lines intramolecular disulfide bridges. The precursor contains one N-linked glycosylation site, indicated by the black diamond

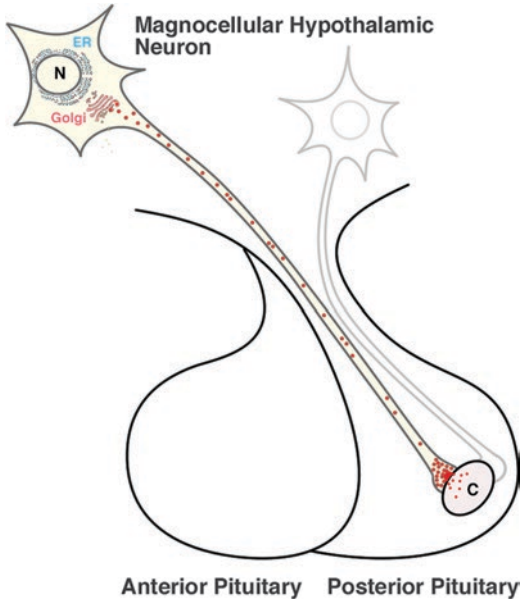

Fig. 9.2 Synthesis, axonal transport, and regulated secretion of AVP. A schematic of a magnocellular neuron with the nucleus (N), endoplasmic reticulum (ER; blue), and Golgi apparatus (red) is shown. The prepro-hormone is synthesized into the ER lumen, where the signal sequence is cleaved, the precursor folds, and glycosylation occurs. After transport through the Golgi apparatus, the prohormone self-aggregates in the trans-Golgi network and forms secretory granules (red dots), which are transported along axons extending to the posterior pituitary. During this transport, proteolytic processing occurs, yielding AVP, NPII, and copeptin. The granules are stored within the nerve endings and fuse with the plasma membrane after an electrical trigger precipitated by an appropriate stimulus (e.g., hyperosmolality). This leads to secretion of the three proteins into neighboring capillaries (C)

through other aquaporin channels located at the basolateral membrane. This urine-concentrating mechanism is very sensitive and also very dynamic due to the short half-life of AVP, allowing rapid responses to changes in blood volume and osmolality. (It is interesting to note that AVP is one of the most potent vasoconstricting molecules, but this effect is mediated by another receptor, AVPR1. Due to the many other vasoconstrictor substances in the body, the absence of AVP, however, is not manifested by defects in vasoconstriction.)

There is a broad differential diagnosis of DI (Table 9.1), which may be caused by one of four basic pathomechanisms. In central or pituitary (neurohypophyseal) DI, synthesis and secretion of AVP is decreased or absent, most often due to a local destructive or infiltrating process. Nephrogenic DI, on the other hand, results from impaired response of the kidney to AVP. In adults, nephrogenic DI is usually acquired and often reversible, e.g., as a consequence of tubular ischemia or transient conditions that alter the sensitivity of the AVPR2, such as electrolyte disorders (hypokalemia, hypercalcemia) or certain drugs. Idiopathic and genetic forms occur in both pituitary and renal DI.

In gestational DI, circulating AVP levels are decreased due to the degradation by a placental vasopressinase. Polyuria and polydipsia may manifest in the absence of other disorders, but preexisting subclinical DI may also be unmasked during pregnancy, prompting a first diagnosis of underlying pituitary or nephrogenic DI. The fourth type of DI is primary polydipsia, which is caused by physiologically suppressed AVP secretion owing to habitual intake of large quantities of fluid. This may occur in the context of psychiatric illness (psychogenic DI) or due to increased thirst sensation (dipsogenic DI).

How do we diagnose DI?

After a detailed medical history, the first diagnostic step is always to confirm the presence of hypotonic polyuria. This is particularly important, since patients tend to misjudge the amount of urine they void. They should therefore be instructed on how to correctly collect a 24-hour urine sample and ideally also quantify their p.o. liquid intake. Various definitions of polyuria exist. In adults, it is generally defined as the production of >45–50 ml urine/kg body weight in 24 hours under *ad libitum* fluid supply. If this is the case solute diuresis is excluded, and the 24-hour urine osmolality is <300 mOsm/kg, the diagnosis is confirmed. The next step is to differentiate which of the DI types is present. In this

Table 9.1 Differential diagnosis of diabetes insipidus

DI type	Underlying causes
Pituitary/ neurohypophyseal	Head trauma, operations Neoplastic disease (e.g., malignant metastases, germinoma, craniopharyngioma, pituitary adenoma) Infections Ischemia (e.g., Sheehan's syndrome) Hemorrhage Autoimmune disease (e.g., neurohypophysitis, lupus erythematosus) Granulomatous disorders (sarcoidosis, histiocytosis) Congenital malformations Brain edema (e.g., brain death) Hereditary Idiopathic
Renal	Ischemic tubulopathy (e.g., tubular necrosis; sickle cell crisis) Drug-induced (e.g., lithium; aminoglycosides, cisplatin) Electrolyte disorders: hypokalemia, hypercalcemia Post-obstructive (transient tubular damage) Infiltrating disorders (e.g., amyloidosis, sarcoidosis) Malignancy Hereditary Idiopathic
Gestational	Increased AVP degradation by placental vasopressinase
Primary polydipsia	Increased thirst in somatic illness (dipsogenic; e.g., meningitis, sarcoidosis, multiple sclerosis) Excessive habitual drinking in mental illness (psychogenic; e.g., schizophrenia, obsessive-compulsive disorder) Increased fluid intake in healthy individuals (lifestyle habit, e.g., in health-conscious persons)

respect, it is important to realize that the picture is not always black and white. As indicated in our case presentation, partial forms of both central and nephrogenic forms exist. These patients can concentrate their urine to a certain degree (typically to less than ~2.5-fold the concomitant serum osmolality), but not enough to preclude polyuria. To complicate things further, chronic polyuria hampers even the healthy kidney's capacity to concentrate the urine, because prolonged high fluid throughput reduces the corticomedullary osmogradient needed for maximum AVP-driven water reabsorption (so-called washout phenomenon).

? What is the classical test to diagnose DI?

✓ Depending on the patient's history (e.g., polyuria following pituitary surgery; DI manifesting de novo in pregnancy; DI in children), it may be unnecessary or even dangerous to perform formal testing. In pituitary and renal DI, random plasma sodium concentrations tend to be high, whereas borderline hyponatremia is expected in primary polydipsia. These values are of course insufficient for a reliable diagnosis, and a standard test is often needed.

✓ The idea is to stimulate the antidiuretic system by inducing a hyperosmolar state and to assess the renal response to this stimulus by measuring urine output and osmolality. Traditionally, the indirect water deprivation

test, with or without infusion of hypertonic saline, has been performed. Body weight, urine excretion, and plasma and urine osmolalities are measured every hour throughout the test. All fluids are refrained until a plasma osmolality of ≥300 mOsm/kg or sodium concentration of ≥150 mmol/L is reached (exact cutoffs vary in different protocols); if necessary, hypertonic saline is infused to reach these values. Failure to concentrate the urine above 300 mOsm/kg despite adequate osmotic stimulation confirms a severe defect in antidiuresis.

How can we differentiate between pituitary and nephrogenic DI?

Synthetic AVP is injected at the end of the test, and the effect on urine volume and osmolality are again measured. If urine osmolality increases by at least 50% after synthetic AVP administration, the diagnosis of pituitary DI can be established.

Is direct testing using AVP measurements useful in the diagnosis of DI?

The interpretation of the indirect test may be difficult, not least because there is large overlap of urine osmolalites between partial DI forms and primary polydipsia. AVP measurements have therefore been advocated to increase diagnostic accuracy. However, preanalytic requirements are cumbersome, and reliable AVP assays, such as published radioimmunoassays used by specialized research laboratories, are not readily available. Moreover, AVP concentrations also show overlap in patients with primary polydipsia and partial pituitary or renal DI. For these reasons, AVP measurements have not been introduced into clinical routine in most hospitals and outpatient clinics.

What are promising novel diagnostic approaches?

As opposed to AVP, copeptin is stable *ex vivo* and can be readily measured in serum or plasma samples with a commercially available enzyme-linked immunosorbent assay. Since copeptin is stoichiometrically co-secreted with AVP, its concentration in the blood serves as useful surrogate marker for circulating AVP. Consequently, recent publications have established copeptin-based diagnostic procedures. High baseline serum/plasma levels (>21.4 pmol/L) are diagnostic for renal DI, making further stimulatory tests unnecessary. In differentiating central DI from primary polydipsia, strenuous thirsting can be avoided if hyperosmolality is induced by intravenous infusion of hypertonic saline; copeptin levels are >4.9 pmol/L in primary polydipsia, but lie below this value in central DI, yielding a high diagnostic accuracy. Even more elegantly perhaps, the antidiuretic system can be stimulated using the arginine infusion test, which is traditionally applied for evaluation of the growth hormone reserve. Using specific baseline and stimulated copeptin cutoff values, the various forms of DI can be distinguished, again with high accuracy.

A detailed overview over the various stimulation tests in the diagnosis of DI is given in the references by Timper et al. [10], Fenske et al. [6], and Winzeler et al. [11].

Stimulation tests are elaborate – is there no easier way to a diagnosis?

Plasma samples for measuring baseline copeptin plasma concentrations can be obtained during outpatient visits. Of the abovementioned stimulatory tests, the arginine infusion test might prove to be feasible for office use. Procedures involving hyperosmolality are potentially dangerous, usually necessitating hourly blood sampling and patient monitoring in a hospital-based setting. In selected adult patients without random hypernatremia, as was the case in our patient described above, but with a random copeptin concentration of <21.4 pmol/L, an overnight thirst test might be undertaken. The patient refrains from drinking after 22–24 hours until the office visit early next morning. No urine collection is needed; the first morning urine portion is voided

at home. In the office, serum or plasma sodium and osmolality are measured, along with the osmolality in the simultaneously obtained second urine portion. It is important to collect this portion shortly after the first void at home, since concomitant serum or plasma and urine osmolalities are needed for correct interpretation. Provided adequate stimulation (as evidenced by serum/plasma osmolality >300 mOsm/kg and/or sodium concentration >150 mmol/L), a urine osmolality below ~2.5-fold that in plasma or serum confirms a defect in antidiuresis. The serum/plasma copeptin concentration can then be used to differentiate between primary polydipsia and central DI. It should be stressed, however, that this overnight testing is not without risk of dehydration and hyperosmolality; it is not indicated in children. Also, in the case of partial antidiuretic failure, an adequate stimulus may not be achieved, making subsequent formal testing necessary. Considering these caveats and constraints, the overnight thirst test should certainly not be the diagnostic standard.

What is the role of imaging in diagnosing neurohypophyseal DI?

In most healthy subjects, the posterior pituitary appears as a hyperintense structure on native T1-weighted MRÌ. The signal is believed to result from neurovesicles stored in the endings of vasopressinergic neurons. Typically, but not universally, this so-called "bright spot" is lacking in patients with pituitary DI (Fig. 9.3). Notably, however, its prevalence decreases with age in normal individuals. Thus, absence of the "bright spot" may be a useful aspect in the workup of polyuria/polydipsia, but it is neither sensitive nor specific enough to base the diagnosis of central DI on this finding alone.

Apart from revealing imaging characteristics of the neurohypophysis, MRI of the hypothalamus/pituitary region is performed to identify potential causes of central DI, e.g., suprasellar or sellar masses or thickening of the infundibulum, as in lymphocytic infundibulo-neurohypophysitis and other disorders.

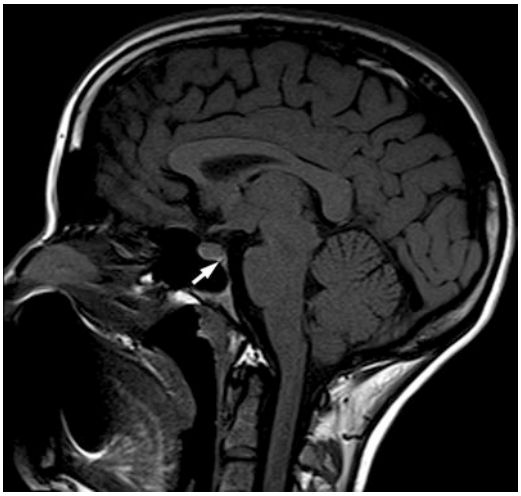

Fig. 9.3 Sagittal T1-weighted native magnetic resonance image of a 28-year-old female with familial neurohypophyseal diabetes insipidus. A small "bright spot" is clearly present (white arrow), despite clinical symptoms and a genetic cause confirmed by mutational analysis

What are general aspects in the treatment of DI?

It is important to make the correct differential diagnosis in polyuria/polydipsia syndrome, because treatment strategies in terms of fluid management are converse in pituitary and nephrogenic DI (ample fluids must be available) as opposed to primary polydipsia (fluid restriction should be pursued). Choosing the correct treatment path is essential to avoid situations of severe de- or hyperhydration, which may be dangerous for the patient. Whether DI is complete or partial, i.e., whether the urine concentrating mechanism is completely abolished or remains partially intact, does not change the general therapeutic strategy. Theoretically, pharmacological therapy is not mandatory as long as ad libitum access to fluids is granted. However, daily urine volume may reach up to ~20 liters in severe forms of DI, necessitating drug treatment, particularly if DI onset is sudden, such as after brain trauma damaging the pituitary gland.

How should renal DI be treated?

In many instances, renal DI is functional and transient in nature, and treatment focuses primarily on fluid replacement and management of electrolyte disturbances. If it is possible to eliminate underlying causes, polyuria will subside spontaneously, which may take weeks in the case of tubulopathy due to ischemic or toxic impact. If persisting DI is present, the situation is more challenging, since – unlike in pituitary DI – there is no specific replacement therapy available. The basic strategy consists of adequate fluid supply on the one hand and the attempt to reduce fluid loss on the other. A thiazide diuretic may be administered, which seems counterintuitive but will result in mild chronic dehydration and thus reduction of the glomerular filtration rate (GFR) and at the same time maximal stimulation of the potentially remaining antidiuretic capacity. Nonsteroidal anti-inflammatory drugs, e.g., indomethacin, increase epithelial water permeability, resulting in an AVP-synergistic effect. They also cause vasoconstriction in the vas afferens of the glomerulum, thereby reducing the GFR and promoting salt and water reabsorption in distal segments of the nephron. Obviously, these pharmacologic approaches do not represent a causative treatment, and the renal function must be closely monitored. Lithium-induced nephrogenic DI, in which the abundance of aquaporin-2 molecules is decreased, is treated with hydrochlorothiazide and amiloride, taking advantage of the apparent amiloride-mediated inhibition of lithium influx into collecting duct cells through epithelial sodium channels.

In the case of inherited (X-linked) nephrogenic DI due to the retention of mutated AVPR2 molecules in the endoplasmic reticulum (ER), cell-permeable AVP antagonists have been used as pharmacological chaperones in cell culture and small clinical studies, promoting ER escape and insertion of the receptor in the basolateral cell membrane. Although promising, this approach has not been introduced into clinical routine.

What is the treatment for pituitary DI?

The synthetic AVP analog 1-desamino-8-D-arginine-vasopressin (DDAVP; desmopressin) is the drug of choice. DDAVP is available as nasal spray or drops, regular tablets, or sublingual "melt" tablets. The injectable formulation is used for diagnostic purpose in the water deprivation/hypertonic saline test, as described above. As compared to the physiological AVP molecule, DDAVP has much less vasoconstrictor effects and an extended half-life of ~2–5 to 4.5 hours. In autosomal dominant neurohypophyseal DI, symptoms manifest subtly and develop gradually over months to years before finally severe disease is present. There have been reports on patients with this form of DI who have grown accustomed to polyuria and therefore do not receive regular treatment, using DDVP only if indicated for social reasons.

What are treatment options for primary polydipsia?

Since urinary output capacity depends on urinary solute excretion, a well-balanced nutrition is important to avoid potentially harmful hyponatremia. Fluid restriction is the causative therapy in primary polydipsia, which is obviously difficult to achieve due to the nature of the disorder. Underlying diseases promoting dipsogenic DI by affecting the hypothalamic thirst mechanism should be treated. Drugs such as propranolol or bupropion have been suggested to reduce polydipsia, but there is little high-quality evidence on treatment options in psychogenic DI. Tolvaptan, a non-peptide AVPR2 antagonist (also evaluated in the treatment of vasopressin overproduction; see next chapter), has been reported to correct hyponatremia in schizophrenic patients, but there are no large trials available to warrant routine use of this treatment. Antipsychotic drugs may reduce the urge to drink resulting from schizophrenia or obsessive-compulsive disorder; on the other hand, common anticholinergic side effects of antipsychotic substances include

dryness of the mouth, which increases the thirst sensation. In these cases, regular moistening should be pursued.

What are the caveats and complications in the management of DI?

As mentioned above, a critical point is the correct distinction between primary polydipsia and the other forms of DI, in which fluid restriction would be detrimental. Patients with psychogenic polydipsia and attacks of binge drinking are in danger of water intoxication and the central nervous complications of acute hyponatremia (altered mental state, seizures, coma, even death). Acute illnesses with extensive loss of fluids (diarrhea, vomiting, febrile states) and high ambient temperatures can lead to dehydration and hypernatremia if liquid intake does not match the deficit and if, in case of central DI, DDAVP doses are not adjusted accordingly. Patients in whom the thirst mechanism is damaged are especially prone to hypo- and hypernatremic complications. If thirst perception is intact, we advise patients to drink in accordance with thirst sensation, rather than ahead, in order to avoid water intoxication. Infants with neonatal DI are especially endangered for acute, potentially lethal dehydration, particularly if there is no initial suspicion of DI because of absent family history.

What do we know about genetic forms of DI?

There are several monogenic types of hereditary DI, all of which are quite rare. The most common among them is X-linked nephrogenic DI due to mutations in the gene encoding AVPR2, but mutations in the *aquaporin-2* gene with autosomal recessive or dominant transmission have very rarely been described. Hereditary central DI is caused by mutations in the *AVP* gene and is most commonly inherited in an autosomal dominant fashion; recessive disease is exceedingly rare. A genetic basis for DI should be considered in every child or young adult in whom signs and symptoms occur without evident cause. This is true even in patients without a family history, because mutations can occur *de novo*. Genetic testing is always advised if a hereditary cause is possible, as well as in siblings of affected patients.

Genetically determined DDAVP-responsive DI may also be a component of a disorder called Wolfram syndrome or DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, deafness), a complex, progressive neurodegenerative disease resulting from mutations in the wolframin (*WFS-1*) gene. Recently, mutations in the gene encoding proprotein convertase subtilisin/kexin type 1 (PCSK1) have been identified in children with diarrhea and various endocrine disorders, among them DDAVP-sensitive DI.

A more in-depth overview over the genetic forms of DI is given in the references by Christensen et al. [5], Bichet and Bockenhauer [2], and Spiess et al. [9].

Tips

The reader is advised to read the chapter on hypopituitarism (▶ Chap. 6) and the subsequent chapter on the syndrome of antidiuretic hormone overproduction and management of hyponatremia.

Take-Home Messages

- There are four basic forms of diabetes insipidus: pituitary (central) DI due to inadequate production and release of AVP; nephrogenic DI due to impaired sensitivity of the kidney to the antidiuretic action of AVP; primary polydipsia, in which AVP secretion is physiologically suppressed by excessive fluid intake; and gestational DI, resulting from enzymatic degradation of AVP by placental vasopressinase.

- The presence of hypotonic polyuria (24-hour urine production >45–50 ml/kg body weight; urine osmolality <300 mOsm/kg) proves a severe defect in antidiuresis.
- Formal stimulatory tests by water deprivation and/or hypertonic saline infusion should be performed in a hospital setting; in selected patients, an overnight thirst test may be warranted.
- The diagnosis or exclusion of primary polyuria is important, since water deprivation should be pursued, which would be contraindicated and potentially dangerous in pituitary or nephrogenic DI.
- Nephrogenic and pituitary DI can be differentiated from primary polydipsia by measuring baseline and stimulated plasma or serum copeptin levels, respectively.
- Pituitary DI is treated with the synthetic AVP analog DDAVP. Therapy of persisting nephrogenic DI is more challenging; drugs used in this setting include nonsteroidal anti-inflammatory agents, thiazide diuretics, and amiloride.
- Hereditary forms of DI should be considered in symptomatic infants and young adults, even in the absence of a family history. Untreated neonatal nephrogenic DI can lead to rapid, potentially lethal dehydration.
- If hereditary DI is considered possible or likely, genetic testing should be performed.

Suggested Reading

1. Adams NC, Farrell TP, O'Shea A, O'Hare A, Thornton J, Power S, Brennan P, Looby S. Neuroimaging of central diabetes insipidus—when, how and findings. Neuroradiol. 2018;60:995–1012. https://doi.org/10.1007/s00234-018-2072-7.
2. Bichet DG, Bockenhauer D. Genetic forms of nephrogenic diabetes insipidus (NDI): vasopressin receptor defect (X-linked) and aquaporin defect (autosomal recessive and dominant). Best Pract Res Clin Endocrinol Metab. 2016;30:263–76. https://doi.org/10.1016/j.beem.2016.02.010.
3. Bockenhauer D, Bichet DG. Pathophysiology, diagnosis and management of nephrogenic diabetes insipidus. Nat Rev Nephrol. 2015;11:576–88. https://doi.org/10.1038/nrneph.2015.89.
4. Christ-Crain M, Bichet DG, Fenske WK, Goldman MB, Rittig S, Verbalis JG, Verkman AS. Diabetes insipidus. Nat Rev Dis Primers. 2019;5(1):54. https://doi.org/10.1038/s41572-019-0103-2.
5. Christensen JH, Rittig S., Weiss RE, Refetoff S. Chapter 5 Diabetes insipidus (2016) In: Weiss RE, Refetoff S. Genetic diagnosis of endocrine disorders, 2nd edition, Elsevier. Saint Louis, 93–101. doi: https://doi.org/10.1016/B978-0-12-800892-8.00005-1
6. Fenske W, Refardt J, Chifu I, Schnyder I, Winzeler B, Drummond J, Ribeiro-Oliveria A Jr, Drescher T, Bilz S, Vogt DR, Malzahn U, Kroiss M, Christ E, Henzen C, Fischli S, Tönjes A, Mueller B, Schopohl J, Flitsch J, Brabant G, Fassnacht M, Christ-Crain M. A copeptin-based approach in the diagnosis of diabetes insipidus. N Engl J Med. 2018;379:428–39. https://doi.org/10.1056/NEJMoa1803760.
7. Robertson GL. Diabetes insipidus: differential diagnosis and management. Best Pract Res Clin Endocrinol Metab. 2016;30:205–18. https://doi.org/10.1016/j.beem.2016.02.007.
8. Sailer CO, Winzeler B, Christ-Crain M. Primary polydipsia in the medical and psychiatric patient: characteristics, complications and therapy. Swiss Med Wkly. 2017;147:w14514. https://doi.org/10.4414/smw.2017.14514.
9. Spiess M, Beuret N, Rutishauser J. Genetic forms of neurohypophyseal diabetes insipidus. Best Pract Res Clin Endocrinol Metab. 2020. in press.
10. Timper K, Fenske W, Kühn F, Frech N, Arici B, Rutishauser J, Kopp P, Allolio B, Stettler C, Müller B, Katan M, Christ-Crain M. Diagnostic accuracy of copeptin in the differential diagnosis of the polyuria-polydipsia syndrome: a prospective multicenter study. J Clin Endocrinol Metab. 2015;100:2268–74. https://doi.org/10.1210/jc.2014-4507.
11. Winzeler B, Cesana-Nigro N, Refardt J, Vogt DR, Imber C, Morin B, Popovic M, Steinmetz M, Sailer CO, Szinnai G, Chifu I, Fassnacht M, Christ-Crain M. Arginine-stimulated copeptin measurements in the differential diagnosis of diabetes insipidus: a prospective diagnostic study. Lancet. 2019;394:587–95. https://doi.org/10.1016/S0140-6736(19)31255-3.

Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH, SIAD) and the Clinical Management of Hyponatremia

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Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_10

Opening

Oversecretion of antidiuretic hormone (ADH, vasopressin) is a common cause of hyponatremia in both hospitalized and ambulatory patients. In the physiological setting, antidiuretic hormone is produced by the hypothalamus and released by the posterior pituitary. However, ADH can also be secreted by tumors as a paraneoplastic endocrine syndrome, or can be increased due to various pathologic processes and use of drugs. This chapter discusses hyponatremia, its clinical management, and the syndrome of inappropriate ADH secretion.

Definition of the Disease

Hyponatremia, defined as serum sodium concentration (SNa^+) < 135 mmol/L, is the most common electrolyte abnormality in clinical practice. Its prevalence reported in hospitalized patients ranges between 6% and 42%, depending on age and underlying disease. Hyponatremia is present in 15–20% of emergency admissions to hospital and occurs in up to 20% of critically ill patients. This electrolyte disturbance can lead to a wide spectrum of symptoms and is associated with substantial morbidity, mortality, and length of hospital stay.

Since serum sodium is the main determinant of plasma osmolality, hyponatremia usually indicates hypoosmolality and hypoosmotic state.

10

Case Report

A 55-year-old man, smoker, was admitted to our Department of Internal Medicine because of unconsciousness. His previous medical history included hypertension and primary hypothyroidism (► Chap. 11) treated with levothyroxine in the dose of 50 μg daily. On physical examination, the patient was eupneic with typical dry and pale skin. Physical examination of the heart and lung did not reveal pathology, heart rate was 76/min, and blood pressure was 150/100 mmHg. Liver and spleen were not palpable and no leg edemas were detected.

Laboratory investigations demonstrated profound hyponatremia (121 mmol/L) and mild hypokalemia (3.5 mmol/L). Plasma osmolality (POsm) was decreased (257 mOsm/kg), while urine osmolality (Uosm 356 mOsm/kg) and urine sodium (61 mmol/L) were higher. The serum level of TSH was increased, reflecting insufficient levothyroxine substitution (TSH 28.9 mIU/L).

How can we determine serum or plasma osmolality?

Sodium, the most abundant electrolyte in the extracellular space, is the major factor of plasma osmolality. Under physiological conditions, the osmolality of body fluid is maintained within narrow limits in each individual by osmotically regulated vasopressin (AVP) secretion and thirst. Although plasma osmolality (POsm) may vary among individual subjects, the range in the general population at normal hydration is between *280 and 295 mOsm/kg* H_2O. POsm can be measured, or alternatively it can be indirectly calculated from the concentrations of sodium, glucose, and blood urea nitrogen:

POsm (mOsm/kg) = $2Na^+ + 2\ K^+$ + *glucose* + *urea* (all in mmol/L)

The terms hyponatremia and hypoosmolality are usually synonymous as the sodium and its accompanying anions represent the main effective plasma solutes. However, there are some situations in which hyponatremia does not reflect true hypoosmolality.

1. *Pseudohyponatremia*, which is defined as spuriously low SNa^+ due to the presence of increased plasma lipid and/or increased plasma proteins. Despite hyponatremia, the increased levels of lipids or proteins do not change the total number of solute particles in solution, and therefore directly measured plasma osmolality will not be significantly changed.
2. *The second situation* occurs in cases with high concentration of effective solutes other than Na^+. This is commonly seen in patients with hyperglycemia and represents a frequent cause of hyponatremia in hospitalized subjects.

How is hyponatremia classified?

There are several aspects on how to classify hyponatremia. In clinical practice, the classification *based on volume status* is most commonly used for the differential diagnosis of hyponatremic states (Table 10.1).

Based on biochemical severity, hyponatremia can be classified into:
(a) Mild hyponatremia (SNa^+ between 130 and 135 mmol/L)
(b) Moderate hyponatremia (SNa^+ between 125 and 129 mmol/L)
(c) Profound hyponatremia ($SNa^+ < 125$ mmol/L)

Based on time course, hyponatremia can be classified as acute and chronic, with the cutoff time duration of 48 h. If the hyponatremia cannot be classified, it is considered chronic, unless there is clinical or anamnestic evidence of the contrary.

According to the clinical practice guideline, drugs and conditions associated with acute hyponatremia include postoperative phase, polydipsia, exercise, recent thiazide prescription, colonoscopy preparation, intravenous administration of cyclophosphamide, oxytocin, and recently started desmopressin or terlipressin therapy [11].

What are the major characteristics of the syndrome of inappropriate arginine vasopressin (antidiuretic hormone) secretion (SIADH)?

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the most common cause of hyponatremia in inpatients. It is defined by an inappropriate release of ADH/AVP or an increased renal response to this hormone. According to the fact that not all the affected patients show elevated circulating levels of AVP, the *term "syndrome of inappropriate antidiuresis" (SIAD)* was proposed as being more accurate. From the clinical viewpoint, the most important clinical abnormality in SIAD is serum hypoosmolality.

The secretion of vasopressin is influenced by various osmotic and non-osmotic stimuli. Under physiological conditions, the effective osmotic pressure in plasma, expressed as serum or plasma osmolality,

Table 10.1 Classification of hyponatremia based on volume status

Hypovolemic hyponatremia	Euvolemic hyponatremia	Hypervolemic hyponatremia
Renal solute losses: diuretics, CSWS, mineralocorticoid deficiency, salt-wasting nephropathy *Extrarenal solute losses:* vomiting, diarrhea, skin losses, burns, acute pancreatitis	SIADH Glucocorticoid deficiency Hypothyroidism	Congestive heart failure Liver cirrhosis Nephrotic syndrome Malnutrition Renal failure

CSWS cerebral salt-wasting syndrome

represents the most important stimulus for AVP release. The threshold for vasopressin release cessation corresponds to a plasma osmolality <275 mOsm/kg, while for POsm 284 mOsm/kg or higher, AVP concentration rises linearly. AVP receptors are so sensitive that 1% osmotic variations are sufficient to result in significant modifications in the hormonal secretion.

SIAD is a disorder of sodium and water balance characterized by hypotonic hyponatremia and impaired urinary dilution in the absence of renal disease. The pathophysiological basis of SIAD is an absolute increase in body water resulting in hypoosmolality. SIAD is the most common cause of hypoosmolality among all hypoosmolar patients with a prevalence of 20–40%.

What was the cause of hyponatremia in the case presented?

The criteria for the diagnosis of SIAD are shown in the Table 10.2. The patient fulfilled all essential criteria for SIAD, except for hypothyroidism that was not optimally substituted. To exclude other causes of SIAD, imaging methods were performed during the hospital stay. Chest X-ray, abdominal ultrasound, and CT of the brain did not detect any pathological changes. We considered hypothyroidism as a cause of hyponatremia; thus we increased the dose of levothyroxine to 100 ug daily. Correction of hyponatremia with hypertonic saline has led to a rapid improvement of his consciousness.

Two months later patient was admitted to our department because of severe hyponatremia again with typical neurological symptoms – nausea, headache, and seizures.

Laboratory evaluation revealed profound hyponatremia (108.9 mmol/L), mild hypokalemia (3.5 mmol/L), serum hypoosmolality (221 mOsm/kg), and higher urinary osmolality (364 mOsm/kg). TSH level was in normal range (2.8 mIU/L). The patient fulfilled criteria for SIAD; however, this time hypothyroidism could be ruled out as a cause of hyponatremia.

Table 10.2 Diagnostic criteria for SIAD

Essential criteria	Supplemental criteria
Effective serum osmolality <275 mOsm/kg	Serum uric acid <0.24 mmol/L
Urinary osmolality >100 mOsm/kg	Serum urea <3.6 mmol/L
Clinical euvolemia (no edemas, no dehydration)	Failure to correct hyponatremia after isotonic saline (0.9%) infusion
Urine sodium concentration >40 mmol/L	Fractional sodium excretion >0.5%
Absence of adrenal, thyroid, pituitary, or renal insufficiency	Fractional urea excretion >55%
No recent use of diuretics	Fractional uric acid excretion >12%
	Correction of hyponatremia through fluid restriction

Based on Esposito et al. [1]

Is Edema a feature of SIAD?

In patients with SIAD, there is no expansion of the extracellular fluid volume (ECFV) and no edemas because water retention leads to suppression of aldosterone and increased atrial natriuretic peptide secretion resulting in urine solute excretion. The patient did not present leg edemas or fluid in the third space (ascites, hydrothorax, or hydropericardium) either. Moreover, he was well hydrated without clinical features of dehydration. Hence we considered hyponatremia as euvolemic, fulfilling the criteria for SIAD.

What kind of examinations should be done to explore the cause of SIAD?

After correction of hyponatremia, we started to differentiate the cause of SIAD. A significant proportion of SIAD is paraneoplastic, and the tumors are most often found in the lung. Therefore, despite normal chest X-ray, a lung CT was indicated, and nonspecific noduli in the subpleural region were detected. Hence, we performed an ^{18}FDG-PET scan that showed a tumor of the right lung spreading to the mediastinum and that was associated with mediastinal lymphadenopathy and metastases to bones. Histological evaluation of the tumor removed by thoracic surgery confirmed a neuroendocrine carcinoma of the lung, type small cell carcinoma (SCLC).

What are the most common etiologies of SIAD?

The most important causes of SIAD are listed in the ▶ Box 10.1. They can be divided into five major groups, i.e., paraneoplastic, brain and pulmonary diseases, drug related hyponatremia and other causes. These causes may be associated both with acute or chronic hyponatremia.

The neuroendocrine carcinoma of the lung was postulated to be responsible for the severe hyponatremia in our patient.

What are the clinical manifestations and symptoms of hyponatremia and SIAD?

Clinical manifestations of SIAD are related to hyponatremia and hypoosmolality that are associated with brain edema because of the decreased plasma osmolality. Clinical manifestations include non-neurological and neurological symptoms with a wide individual variability. The severity of symptoms depends on the duration and degree of hyponatremia.

Mild hyponatremia is usually asymptomatic.

Moderate hyponatremia is commonly presented with tiredness, headache, nausea, vomiting, confusion, muscle weakness, or cramping.

Severe hyponatremia is usually manifested by vomiting, somnolence, seizures, or coma.

Recent studies showed that also mild and chronic hyponatremia is never truly asymptomatic and it can be associated with memory disturbances, chronic headache, muscle weakness, or depression. Moreover, studies have demonstrated a higher risk of falls, osteoporosis, and bone fractures in patients with chronic hyponatremia along with higher mortality. Correction of hyponatremia and improvement of serum sodium was significantly associated with a reduced risk of mortality.

How is the differential diagnosis of hyponatremia performed?

The differential diagnosis of hyponatremia is difficult, and no classification can be 100% accurate in every situation. The current guidelines emphasize that classification should always occur along with the clinical condition and the possibility of combined causes of hyponatremia should be kept in mind.

In the first step of differential diagnosis, we should exclude non-hypotonic hyponatremia that is seen in the vast majority of cases with hyperglycemic hyponatremia. Lower serum sodium concentration with a decreased POsm (<275 mOsm/kg) always reflects hypotonic hyponatremia. In case of hypotonic hyponatremia, the current guidelines recommend measuring urine osmolality (UOsm). If UOsm is lower than 100 mOsm/kg, we should consider excess of water intake as a cause of the hypotonic hyponatremia. If UOsm is >100, guidelines recommend interpreting the urine sodium concentration (UNa^+) on a spot urine sample taken simultaneously with a blood sample.

If UNa^+ is ≤30 mmol/L, low effective circulating volume as a cause of hyponatremia should be considered. If UNa^+ > 30 mmol/L, we should assess

Box 10.1 The Most Important Causes of SIAD (*based on* Robinson and Verbalis [9])

Tumors (paraneoplastic syndromes)
- Lung/mediastinal neoplasia (lung cancer (most often small cell carcinoma), mesothelioma, thymus tumor)
- Other tumors (gastrointestinal, e.g., stomach, duodenum, pancreas, head and neck cancer, prostate, ureter, breast, uterus cancer, leukemia)

Lung disorders
- Infections (acute pneumonia (bacterial or viral), tuberculosis, aspergillosis)
- Noninfectious causes (acute respiratory failure, bronchial asthma/chronic obstructive pulmonary disease)

Disturbances of the central nervous system
- Masses and bleedings (brain tumors, abscess, subdural hematoma, subarachnoid hemorrhage, hydrocephalus)
- Inflammation (infectious (meningitis, encephalitis), autoimmune (systemic lupus erythematosus, multiple sclerosis))
- Degenerative/demyelinate diseases
- Other CNS-related causes (acute intermittent porphyria, head trauma, psychosis, pituitary adenomectomy[a])

Drug-related SIAD
- Arginine vasopressin and its analogues
- Thiazide and thiazide-like diuretics
- Chlorpropamide
- Antipsychotics – risperidone, haloperidol, chlorpromazine, olanzapine, etc
- Antidepressants – citalopram, escitalopram, amitriptyline, etc.
- Anticonvulsants – carbamazepine, phenytoin, valproate, etc.
- Cytotoxic agents – vincristine, vinblastine, cyclophosphamide
- Pain medication – morphin, duloxetine, pregabalin, tramadol, oxycodone
- Nonsteroidal anti-inflammatory drugs
- Oxytocin
- Nicotine
- Proton-pump inhibitors, amiodarone

Other causes
- Acquired immunodeficiency syndrome, prolonged exercise

[a]SIAD after pituitary adenomectomy is usually transient

extracellular fluid status and use of diuretics for further differentiation. In clinical practice, considering primary or secondary adrenal insufficiency as an underlying cause of the hypotonic hyponatremia is very important, especially in states with hyperkalemia (Figs. 10.1 and 10.2).

Should plasma AVP be determined for the diagnosis of SIAD?

The current guidelines *do not recommend measurement of AVP* in plasma for confirming the diagnosis of SIAD. AVP is very difficult to measure mainly due to preanalytical and analytical problems. However, *copeptin* as the C-terminal fragment of the pre-pro-vasopressin highly reflects AVP concentrations. The main stimuli for copeptin are similar to AVP, and the peptide is considered as a stable surrogate marker for AVP concentrations in humans. According to a large prospective study with copeptin measurements, clearly elevated copeptin levels indicated hypovolemic hyponatremia (specificity 90%, sensitivity 23%), whereas low levels pointed to primary polydipsia (specificity 91%, sensitivity 58%). Unfortunately, serum copeptin concentration was not helpful to differentiate between SIAD and other causes of hyponatremia. Therefore, the broad use of copeptin as diagnostic marker in hyponatremia cannot be recommended, yet.

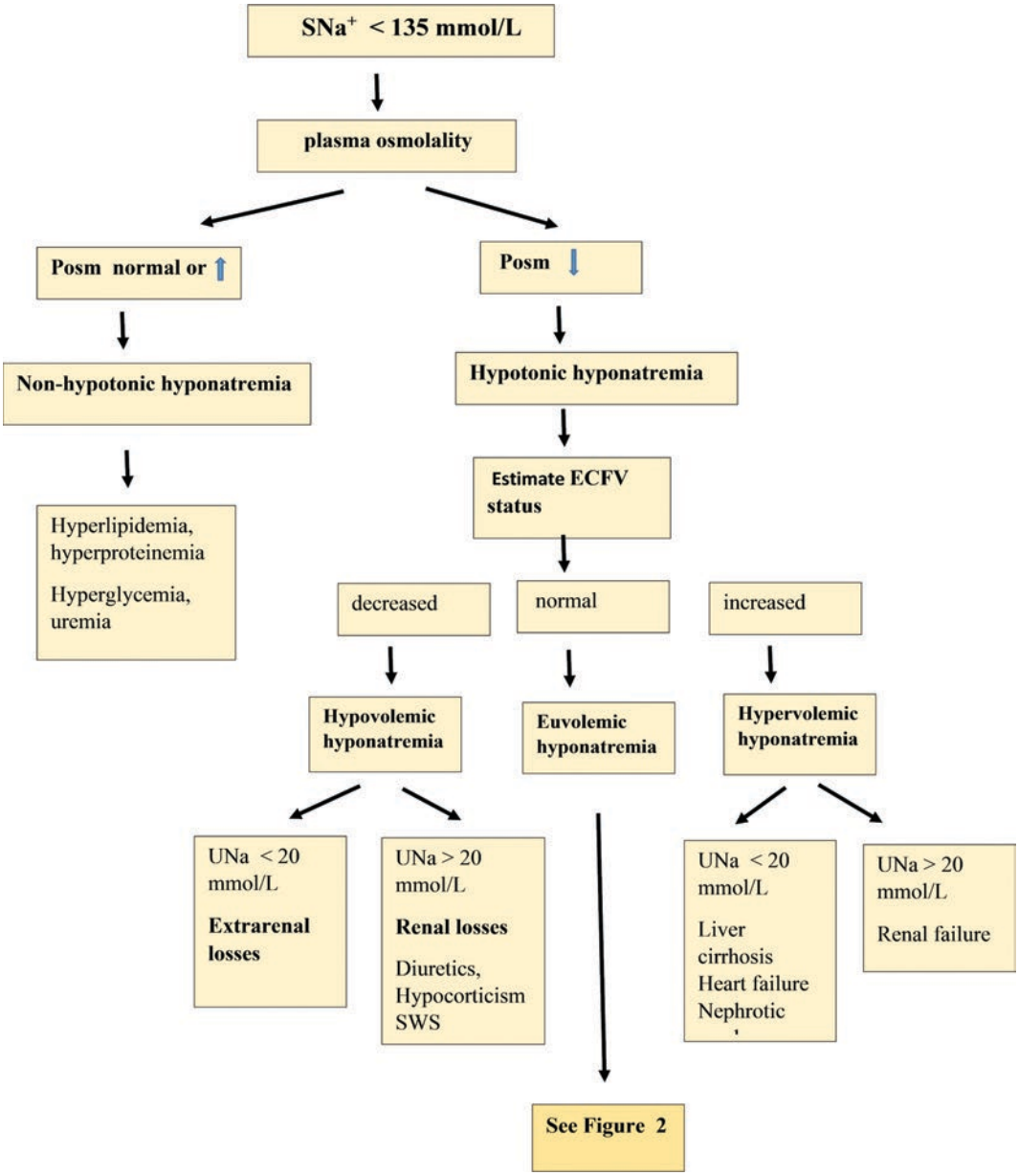

Fig. 10.1 Algorithm for the differential diagnosis of hyponatremia

What are the other major causes of hyponatremia to be considered?

In differential diagnosis, thiazide-induced hyponatremia, salt-wasting syndromes, glucocorticoid deficiency, and mineralocorticoid-responsive hyponatremia in the elderly should be considered.

Thiazide-Induced Hyponatremia (TIH)

Since the demonstration of their antihypertensive effect, thiazides have been widely used in the management of hypertension. However, despite the clinical success of these diuretics, they can cause significant side effects, including hypona-

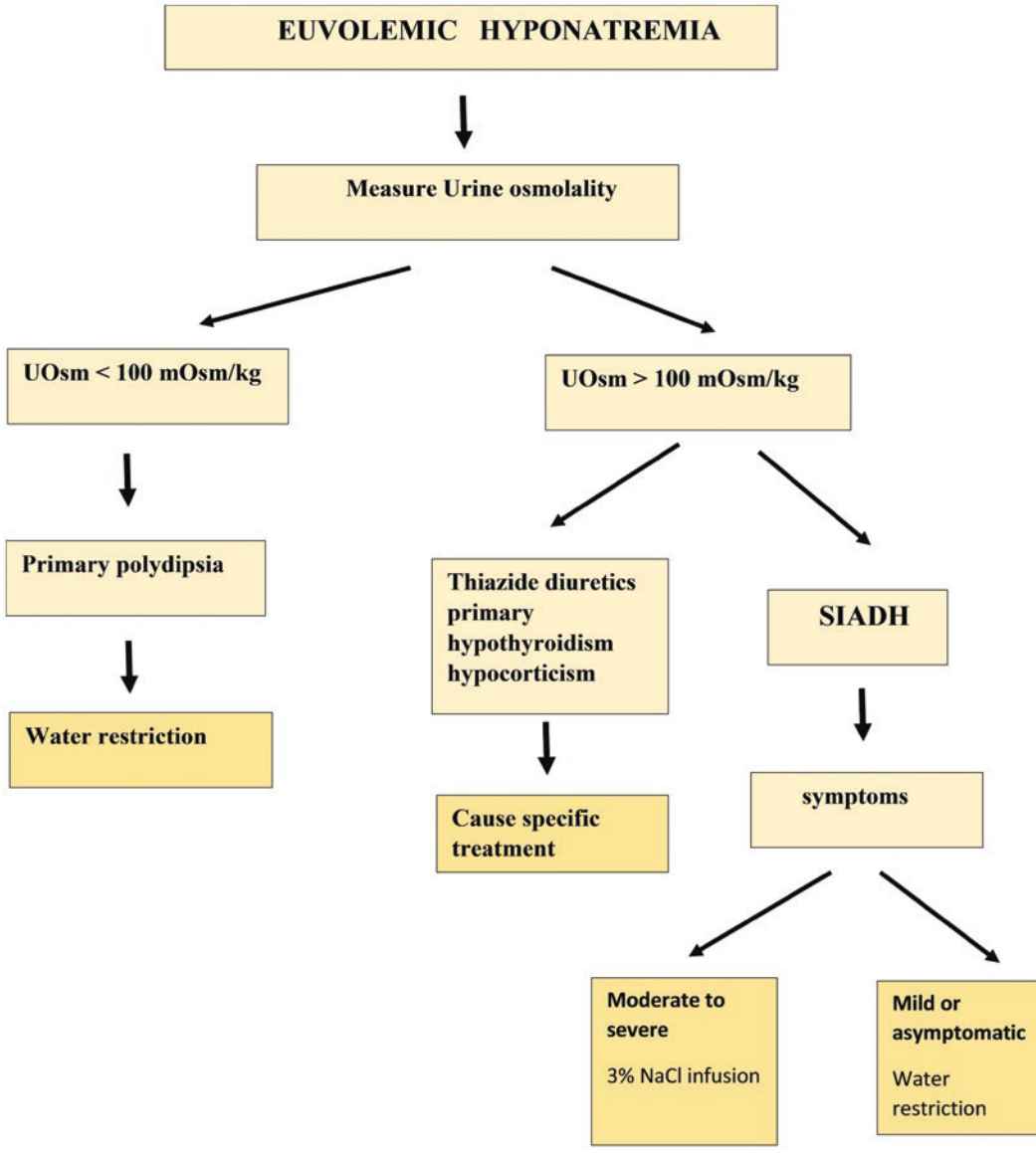

Fig. 10.2 Algorithm for the differential diagnosis and management of euvolemic hyponatremia

tremia. TIH has been reported with many types of thiazide (hydrochlorothiazide) and thiazide-like diuretics (indapamide, chlorthalidone). The reported prevalence is relatively high (from 14% to 38%) and increases with age, which is an independent risk factor for development of TIH.

The risk factors for the development of TIH include age (>70 years), female gender, lower BMI, type 2 diabetes mellitus and other comorbidities (cardiovascular, pulmonary, psychiatric diseases associated with polydipsia, etc.), increased water intake, as well as concomitant administration of other drugs interfering with water homeostasis (spironolactone, amiloride, selective serotonin reuptake inhibitors, nonsteroidal anti-inflammatory drugs, benzodiazepines, proton-pump inhibitors). Hypokalemia and/or lower baseline serum sodium concentration significantly increases the risk for

TIH development. Also, genetic predisposition is supported by recent genome-wide association studies (GWAS).

How should the differential diagnosis of TIH be done?

Similarly to other types of hyponatremia, laboratory investigation should be initiated with the measurement of plasma osmolality (POsm). It is crucial to differentiate non-hypotonic hyponatremia from the true hypotonic hyponatremia. When the latter has been confirmed, serum urea, creatinine, potassium, uric acid, as well as TSH and cortisol levels should be determined. Moreover, urine sodium, potassium, urea, creatinine, and uric acid should also be measured in a spot urine sample, and subsequently fractional excretion (FE) should be calculated.

The diagnosis of TIH is supported by the following findings:

- Coexistent hypokalemia with FE of $S\text{-}K^+ > 13\%$
- Low FE of uric acid (<12%) is usually observed in TIH, whereas FE >12% indicates SIAD
- UNa^+ >30 mmol/L may also indicate TIH.

Salt-Wasting Syndromes

The cerebral and renal salt-wasting syndromes (SWS) require special attention for diagnosis. They are characterized by hyponatremia and ECFV depletion, caused by an abnormal renal sodium excretion mainly in patients with intracranial disease, such as subarachnoid hemorrhage or other lesions. Both SWS and SIAD present with hyponatremia, concentrated urine, and increased natriuresis, but SWS is characterized by ECFV depletion. Differences between SIAD and cerebral salt-wasting syndrome (CSWS) are presented in Table 10.3.

Table 10.3 Differences between SIAD and the cerebral salt-wasting syndrome (CSWS)

	SIAD	CSWS
Blood pressure	N	N/ hypotension
CVP	N	Decreased
UV	N/low	High
UNa^+	>30 mmol/L	>40 mmol/L
Serum urea concentration	N/decreased	N/increased
Serum uric acid	Decreased	Decreased

Based on Spasovski et al. [11]
Abbreviations: *CVP* central venous pressure, *UV* urine volume, *UNa^+* urine sodium concentration, *N* normal

In case of diagnostic uncertainty, correction of hyponatremia with the infusion of 2 liters of 0.9% saline over a period of 24–48 h, suggests a diagnosis of hypovolemic hyponatremia.

Mineralocorticoid-Responsive Hyponatremia of the Elderly (MRHE)

MRHE is characterized by mild hypovolemic hyponatremia due to renal sodium losses in elderly subjects. Age-related decreased sodium reabsorption at proximal renal tubules and hyporesponsiveness of the renin-angiotensin-aldosterone system (RAAS) may cause persistently increased urinary sodium excretion. Decreased sodium retention leads to volume depletion resulting in elevation of plasma antidiuretic hormone. The recommended treatment of MRHE is administration of mineralocorticoid (fludrocortisone acetate), but not water restriction, which can worsen hyponatremia.

Primary and Secondary Adrenocortical Insufficiency

- Slightly decreased ECV is usually observed in patients with primary or secondary adrenocortical insufficiency, which can mimic features of SIAD. ACTH or cortisol deficiency should be ruled out before establishing the diagnosis of SIAD. Glucocorticoid replacement therapy normalizes free water excretion and subsequently serum sodium concentration.

How should the patient with hyponatremia be treated?

Case Presentation Continued

During the first hospital stay, it was decided to increase the dose of levothyroxine simultaneously with an immediate active correction of hyponatremia. The patient received two boluses of 3% saline solution intravenously over 20 min, and after 6 h, his serum sodium concentration raised from 121 mmol/L to 128 mmol/L. This led to a marked improvement in his neurological symptoms. Subsequently, the patient received one bolus of hypertonic saline on the second and the third days of hospitalization resulting in normalization of serum sodium concentration and neurological status as well.

How should hyponatremia be managed depending on its etiology?

- Despite its high incidence and potential risk, the management of SIAD is often insufficient and poor. Factors which should be taken into consideration before making a treatment decision for hypotonic hyponatremia treatment include the severity and duration of hyponatremia, the patient's neurological symptomatology, and extracellular fluid volume status.

- *Hypervolemic hyponatremia* is usually chronic and patients are well-adapted. If the ECFV is expanded, the treatment of the underlying cause should precede the correction of serum sodium level. Fluid restriction is considered to be the first step in the management of the patient. The current guidelines do not recommend prompt correction of serum sodium in mild or moderate hyponatremia and recommend against demeclocycline or vasopressin receptor antagonists.

- The aim of the treatment of *hypovolemic hyponatremia* is to restore extracellular fluid volume with intravenous infusion of isotonic (0.9%) saline. Normal saline is usually used to suppress the hypovolemic stimulus for ADH. It should be reserved for mild symptomatic patients and for those cases where it is difficult to differentiate between hypovolemic and euvolemic status. In case of hemodynamic instability, the need for rapid fluid resuscitation exceeds the risk of a rapid increase in serum sodium concentration.

- *Treatment of Euvolemic Hyponatremia (SIAD)*

- *Acute euvolemic hyponatremia* with severe or moderately severe symptoms requires administration of hypertonic saline solution (3% NaCl, 150 mL or 1–2 mL/kg body weight) over 20 min. Serum sodium concentration should be checked after 1, 6, and 12 h. If seizures or coma are present, infusion can be increased up to 4 mL/kg for a limited period. The clinical practice guideline suggests aiming at a 5 mmol/L/24 h increase in serum sodium. The SNa^+ should not rise at a rate exceeding 10 mmol/L during the first 24 h and an additional 8 mmol/L during the following 24 h. If hypokalemia is present, its correction will contribute to an increase in serum sodium concentration. Treatment with a single intravenous infusion of 150 mL 3% NaCl is recommended also in hyponatremic patients without severe or moderately severe symptoms.

- In addition, all medications and other factors that can provoke or contribute to the hyponatremia should be discontinued, and the diagnostic assessment should be started immediately.

- Furosemide has been reported as an additive treatment for SIAD that could be effective in the initial phase because of its ability of increasing free water excretion. However, the clinical practice guidelines do not include it in the recommendations.

- *Chronic asymptomatic hyponatremia* – arbitrarily defined as more than 48 h in duration – represents less risk regarding complications, but can also be related to demyelination after rapid correction. These patients should be treated with slower-acting options, such as fluid restriction or vasopressin receptor antagonists.

- *Chronic symptomatic hyponatremia* similarly to the acute should be treated promptly, but the rise in serum sodium should not exceed 10 mmol/L in the first 24 h and 18 mmol/L in the first 48 h.

How should chronic hyponatremia be treated in the long-term?

- The treatment of chronic SIAD entails a choice among several options and regimens. All drugs and factors known to be associated with SIAD should be discontinued. Cause-specific treatment is recommended by the clinical practice guideline.

- Fluid restriction of 800–1000 mL/24 h is the mainstay of treatment for mild to moderate SIAD.

- Urea in the dose of 0.25–0.50 g/kg is effective in increasing free water clearance, and it is useful especially in young children affected by SIAD.

- Other options include demeclocycline and lithium (that induce nephrogenous diabetes insipidus and thereby could be helpful against AVP overproduction); however, because of their side effects (especially nephrotoxicity), the clinical practice guidelines recommend against their use in the treatment of chronic hyponatremia in SIAD.

- The use of salt tablets in the treatment of euvolemic hyponatremia was associated with a small but significant improvement in serum sodium compared with patients who did not receive such therapy.

- Non-peptide *vasopressin receptor antagonists* known as *vaptans or aquaretics* block V2 receptors of AVP and decrease aquaporin 2 at renal collecting ducts resulting in urinary free water excretion. The patient presented received tolvaptan along with chemotherapy for the neuroendocrine carcinoma, and his SNa^+ was well-controlled by this treatment protocol. However due to their side effect profile (polyuria, weakness, dehydration, and hepatotoxicity) and cost, their use in the treatment SIAD is still limited and not included in the general recommendations for the treatment of hyponatremia.

What is the danger of correcting hyponatremia too rapidly?

- Osmotic demyelination syndrome (ODS), consisting of central pontine myelinolysis and extrapontine myelinolysis, is associated with the rapid correction of hyponatremia and can be fatal. The susceptibility to demyelination after correction of sodium concentration is influenced by the severity and duration of preexisting hyponatremia. Severe and long hyponatremia is an important risk factor for ODS. Other risk factors are chronic alcoholism, malnutrition, and hypokalemia. The onset of symptoms is usually seen 1–14 days after sodium correction.

What are the clinical features of osmotic demyelination syndrome?

- Clinical features are various and include symptoms of pontine or extrapontine lesions, such as dysphagia, dysarthria, ataxia, or even coma. Although the presence of demyelinating areas on magnetic resonance imaging strongly supports a diagnosis of ODS, scans often fail to dem-

onstrate typical changes in the initial phase, and therefore MR should be repeated within 2–3 weeks.

The treatment of ODS is primarily aimed at prevention. Recent studies have shown that desmopressin has been safe and effective in preventing ODS. The administration of desmopressin with hypertonic saline was associated with a lower incidence of sodium overcorrection. The clinical practice guideline recommends urgent intervention for re-lowering serum sodium if it increases by more than 10 mmol/L during the first 24 h. Administration of desmopressin is recommended in a dose of 1–2 μg intravenously or subcutaneously every 8 h. Discontinuing the ongoing active treatment of hyponatremia is also necessary.

Tips

The reader is advised to read the previous chapter on diabetes insipidus (▶ Chap. 9) and the part on neuroendocrine tumors and paraneoplastic endocrine syndromes.

10

Take-Home Messages

- Hyponatremia is defined as serum sodium concentration <130 mmol/L, and it is the most common electrolyte abnormality in clinical practice.
- Syndrome of inappropriate antidiuresis (SIAD) is the most common cause of euvolemic hyponatremia
- SIAD is characterized by hypotonic hyponatremia and impaired urinary dilution in the absence of renal disease
- Clinical manifestations of SIAD are related to hypoosmolality resulting in brain edema and include non-neurological and neurological symptoms
- Treatment of acute euvolemic hyponatremia with severe or moderately severe symptoms requires administration of hypertonic saline (3%). We should avoid overcorrection of serum sodium because of the risk of pontine and extrapontine myelinolysis.
- Restriction of water intake is considered the first treatment option in the management of chronic hyponatremia

Suggested Reading

1. Esposito P, Piotti G, Bianzina S, Malul Y, Dal Canton A. The syndrome of inappropriate antidiuresis: pathophysiology, clinical management and new therapeutic options. Nephron Clin Pract. 2011;119(1):c62–73; discussion c73. https://doi.org/10.1159/000324653.
2. Filippatos TD, Makri A, Elisaf MS, Liamis G. Hyponatremia in the elderly: challenges and solutions. Clin Interv Aging. 2017;12:1957–65. https://doi.org/10.2147/CIA.S138535.
3. Katayama K, Tokuda Y. Mineralocorticoid responsive hyponatremia of the elderly: a systematic review. Medicine (Baltimore). 2017;96(27):e7154. https://doi.org/10.1097/MD.0000000000007154.
4. Lambeck J, Hieber M, Dreßing A, Niesen WD. Central pontine myelinolysis and osmotic demyelination syndrome. Dtsch Arztebl Int. 2019;116(35–36):600–6. https://doi.org/10.3238/arztebl.2019.0600.
5. Liamis G, Filippatos TD, Elisaf MS. Thiazide-associated hyponatremia in the elderly: what the clinician needs to know. J Geriatr Cardiol. 2016;13(2):175–82. https://doi.org/10.11909/j.issn.1671-5411.2016.02.001.
6. Liamis G, Megapanou E, Elisaf M, Milionis H. Hyponatremia-inducing drugs. Front Horm Res. 2019;52:167–77. https://doi.org/10.1159/000493246. Epub 2019 Jan 15.
7. Peri A, Grohe C, Berardi R, Runkle I. SIADH: differential diagnosis and clinical management. Endocrine. 2017;55(1):311–9. https://doi.org/10.1007/s12020-016-0936-3.
8. Refardt J, Winzeler B, Christ-Crain M. Copeptin and its role in the diagnosis of diabetes insipidus and the syndrome of inappropriate antidiuresis. Clin Endocrinol (Oxf). 2019;91(1):22–32. https://doi.org/10.1111/cen.13991.
9. Robinson AG, Verbalis JG. Posterior pituitary. In: Melmed S, Polonsky KS, Reed Larsen P, Kronenberg HM, editors. Williams textbook of endocrinology. 12th ed. Philadelphia: Saunders, Elsevier; 2011. p. 291–323.

10. Shepshelovich D, Schechter A, Calvarysky B, Diker-Cohen T, Rozen-Zvi B, Gafter-Gvili A. Medication-induced SIADH: distribution and characterization according to medication class. Br J Clin Pharmacol. 2017;83(8):1801–7. https://doi.org/10.1111/bcp.13256.

11. Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, Decaux G, Fenske W, Hoorn E, Ichai C, Joannidis M, Soupart A, Zietse R, Haller M, van der Veer S, Van Biesen W, Nagler E. Clinical practice guideline on diagnosis and treatment of hyponatremia. Intensive Care Med. 2014;40(3):320–31. https://doi.org/10.1007/s00134-014-3210-2.

Diseases of the Thyroid

The thyroid gland produces thyroxine (T**4**) and its active form triiodothyronine (T**3**), which are involved in the regulation of several important homeostatic mechanisms including the regulation of development and metabolism and effects on the heart and bones. Both the overproduction and deficiency for thyroid hormones is related to serious morbidities. Hypothyroidism (mostly caused by Hashimoto's thyroiditis) (► Chap. 11) is the second most common endocrine disease after diabetes mellitus. Graves' disease (hyperthyroidism, ► Chap. 12) and its complications such as endocrine orbitopathy (► Chap. 13) and thyroid storm (► Chap. 14) are presented in separate chapters. Thyroid nodule and multinodular goiter that are among the most common endocrine diseases are discussed in ► Chap. 15. Differentiated thyroid cancer and its complex management is the focus of ► Chap. 18, whereas ► Chap. 19 presents medullary thyroid cancer that originates from calcitonin-producing C-cells of the thyroid. Individual chapters are dedicated to inflammatory conditions of the thyroid (thyroiditis) with major clinical relevance such as subacute thyroiditis (► Chap. 16), amiodarone-induced thyroiditis (► Chap. 17), and postpartum thyroiditis (► Chap. 21). A rare, but very interesting disease, thyroid hormone resistance along with its differential diagnosis from secondary hyperthyroidism (pituitary thyroid stimulating hormone overproduction) is discussed in ► Chap. 20.

Contents

Hypothyroidism and Hashimoto's Thyroiditis

Peter Reismann

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_11

Opening

In this chapter, one of the most frequent endocrine disorders will be discussed. Hypothyroidism – overt or subclinical – is the second commonest endocrine disease after diabetes mellitus. Hypothyroidism is the consequence of insufficient thyroid hormone production and action. It can be primary, secondary, and tertiary hypothyroidism, but primary hypothyroidism is the most common form.

Having read this chapter, the reader will be able to differentiate subclinical and overt, primary, and secondary forms of hypothyroidism and get information on the examination protocols and therapy follow-up possibilities.

Definition of the Disease

Insufficient thyroid hormone production or action leads to subclinical or overt hypothyroidism. If the thyroid is the primarily affected organ that is unable to produce enough hormone, then it is called *primary hypothyroidism*, which is the most common form. If pituitary TSH (thyroid-stimulating hormone) secretion is insufficient, then it is the *secondary* form of *hypothyroidism*. In very rare cases, the hypothalamic TRH (TSH-releasing hormone) secretion is defective, and this form is the *tertiary hypothyroidism*.

Hypothyroidism is overt, when the serum concentration of free T_3 (triiodothyronine) or of free T_4 (L-thyroxine) is under the reference range with symptoms. In primary hypothyroidism, the thyroid gland is unable to produce enough thyroid hormones (mainly T_4); that is why TSH – as a consequence of negative feedback mechanism – will be elevated. If TSH is over the normal reference range, but free T_4 concentration is still in the reference range, that is the so-called *"subclinical" hypothyroidism*. Here TSH acts as a booster on the thyroid gland to produce more thyroid hormones.

In case of pituitary insufficiency (hypopituitarism, ▶ Chap. 6), TSH production is low, and it is accompanied by low free T_4. This is the typical appearance of secondary hypothyroidism. The same is typical for hypothalamic tertiary hypothyroidism. ◘ Figure 11.1 shows the negative feedback mechanism that regulates the hypothalamic-pituitary-thyroid axis.

In the tissues, T_4 is converted to T_3 by deiodinase enzymes (DIO_1 and DIO_3). T_3 is the main active hormone that has several effects on a wide variety of cells in almost every organ. Thyroid hormones can influence the metabolism, function, and proliferation of cells via genomical and non-genomical mechanism.

Mortality and morbidity are increased by overt hypothyroidism. Subclinical hypothyroidism might increase the cardiovascular mortality in patients under 70 years; however, this risk elevation seems to disappear over 70 years.

Epidemiology: The frequency of hypothyroidism depends on the iodine availability (iodine-rich or iodine-deficient soil/nutrition). The incidence and prevalence of hypothyroidism, especially that of subclinical hypothyroidism, are increasing with age. Overt hypothyroidism has an average prevalence of 0,5–2%, while its subclinical form is found in about 4–10% of the population. The frequency of congenital hypothyroidism is 1:4000. The different causes of hypothyroidism are presented in ◘ Table 11.1.

Thyroid dysfunction is more frequent in females (female-male ratio is about 10:1).

Hashimoto's thyroiditis is an autoimmune thyroid disease (AITD). Hakaru Hashimoto described the disease in 1912. Its original name was struma lymphomatosa, because histological examination revealed diffuse lymphocytic infiltration with germinal centers, fibrosis, parenchymal atrophy, and degenerated thyroid epithelial cells. In the middle of the 1950s, Dr. Rose and Witebsky showed that immunization of thyroid extracts can evoke similar pathological changes in rabbit thyroid, that seen in Hashimoto's thyroid-

itis. At the same time, the first antibody was purified, as anti-thyroglobulin. Later, the other main antibody against thyroid peroxidase was detected.

Hashimoto's thyroiditis is an organ-specific autoimmune thyroid disorder with typical structural alterations and the presence of thyroid-specific autoantibodies. The autoimmune process, which destroys the organ, can evoke functional changes, mainly hypothyroidism. The etiological background is complex, including genetic susceptibility, epigenetic effects, and various environmental triggers (iodine, infection, stress, pregnancy). There are two main forms that share the same pathophysiology: goitrous and atrophic.

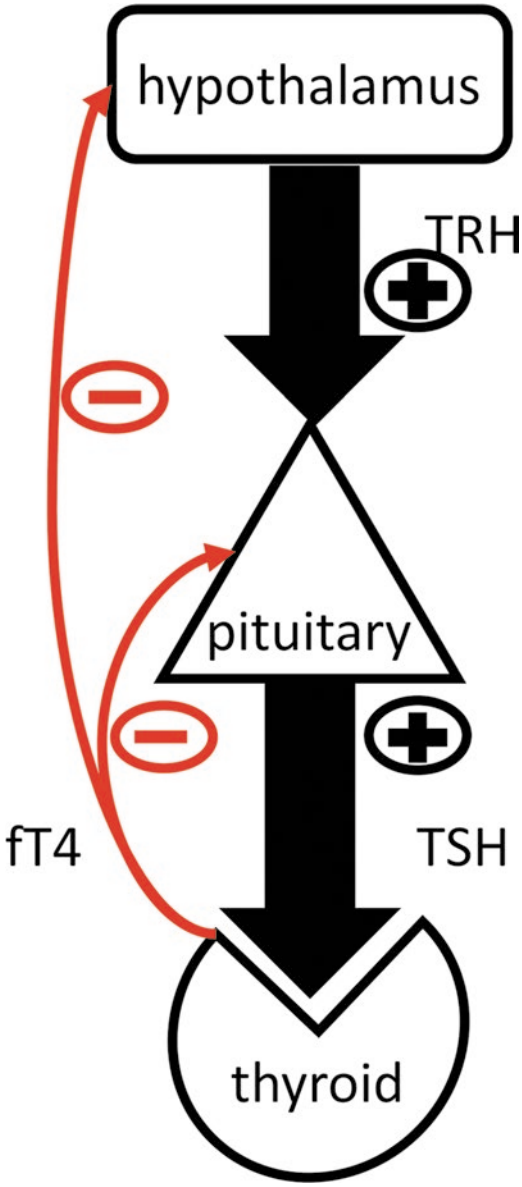

Fig. 11.1 Schematic representation of the hypothalamic-pituitary-thyroid axis

Table 11.1 Causes of hypothyroidism

Congenital hypothyroidism	*Definitive:* thyroid dysgenesis, hormone synthesis defect *Transitional:* iodine deficiency of the mother, blocker TRAb in the mother serum, thyrostatic medication
Primary hypothyroidism	Thyroiditis – lymphocytic autoimmune thyroiditis – Hashimoto's thyroiditis Postpartum thyroiditis, silent thyroiditis
Posttherapeutic reasons:	Thyroid resection ^{131}Iodine ablation therapy Neck External beam therapy
Medication	Thyrostatic drugs, lithium, increased concentration of iodine, amiodarone, interferon, mitotane
Environmental factors	Long-lasting iodine deficiency
Central hypothyroidism	Pituitary (secondary) Hypothalamic (tertiary)

TRAb TSH receptor antibody

Case Presentation

A 34-year-old female patient was admitted to the endocrine outpatient clinic. Her previous medical history was largely negative. Family history was positive for goiter (mother, grandmother). She complained about irregular menses, unsuccessful pregnancy (one spontaneous abortion 10 months before, thereafter no conceiving), weight gain (+15 kg/6 months), sleepiness (sleep up to 10 hours/day), fatigue, leg edema, overall dry skin, increased hair loss, and new hoarseness. Furthermore, she mentioned that her memory has declined, and she was not able to fulfill her job requirements.

Physical examination revealed a proportional obesity, BMI, 31 kg/m^2; body weight, 89 kg; body height, 169 cm; and waist circumference, 91 cm. At inspection dry skin, palpable pretibial slight edema, and sparse eyebrow were noted. The thyroid was enlarged, slightly stuffed, but no nodule was palpable. On pressure a small amount of galactorrhea (breast milk in non-lactating women) appeared from the nipples: RR, 155/100 mmHg; pulse, 65/min.

Which pieces of information are important regarding thyroid dysfunction?

Positive family history is a common hallmark. In female relatives, the higher incidence of thyroid disease is well-known. Typical symptoms of hypothyroidism are mentioned as weight gain, sexual dysfunction (irregular menses, infertility), fatigue, memory problems, and skin cutaneous manifestations of low thyroid hormone availability (Fig. 11.2). Galactorrhea is an uncommon, but potential, symptom of severe hypothyroidism. Table 11.2 presents the typical symptoms.

What is myxedema?

Myxedema, the non-pitting edema of the skin and soft tissues, is a characteristic feature of hypothyroidism, and it is a classical alternative name for the disease. Myxedema is related to the accumulation of glycosaminoglycans retaining water.

What are the essential initial diagnostic steps?

Laboratory Examinations

In general, in patients with intact pituitary function, *TSH* alone is enough to evaluate thyroid functioning. Many laboratories set an automatic process, and if TSH turns out to be above the reference range, fT_4 will be automatic measured. Measuring fT_3 in case of hypothyroidism is not essential. Total T_4 or thyroid-binding globulin is not needed.

Since the patient has a special complaint, i.e., galactorrhea, prolactin measurement is also recommended.

Prolactin can be elevated in overt, primary hypothyroidism. Prolactin secretion is negatively influenced by dopamine and positively by TRH. In case of primary hypothyroidism, via the decreased negative feedback in the thyroid-hypothalamus-pituitary axis, TRH will be increased that stimulates prolactin secretion. Increased prolactin induces galactorrhea and suppresses the gonadotropin (LH/FSH secretion), thus disturbing the menstrual cycle.

Autoimmune Markers

As the most frequent cause of primary hypothyroidism is autoimmune lymphocytic thyroiditis (Hashimoto's thyroiditis), screening for autoimmune origin is recommended. *Thyroid peroxidase autoantibody (aTPO)* is a sensitive marker for it. As a second line, *anti-thyroglobulin antibody (aTG)* can be also measured; however it has a lower sensitivity. Marked positivity of aTPO strengthens the autoimmune root. However, slightly increased aTPO does not have enough sensitivity for diagnosis.

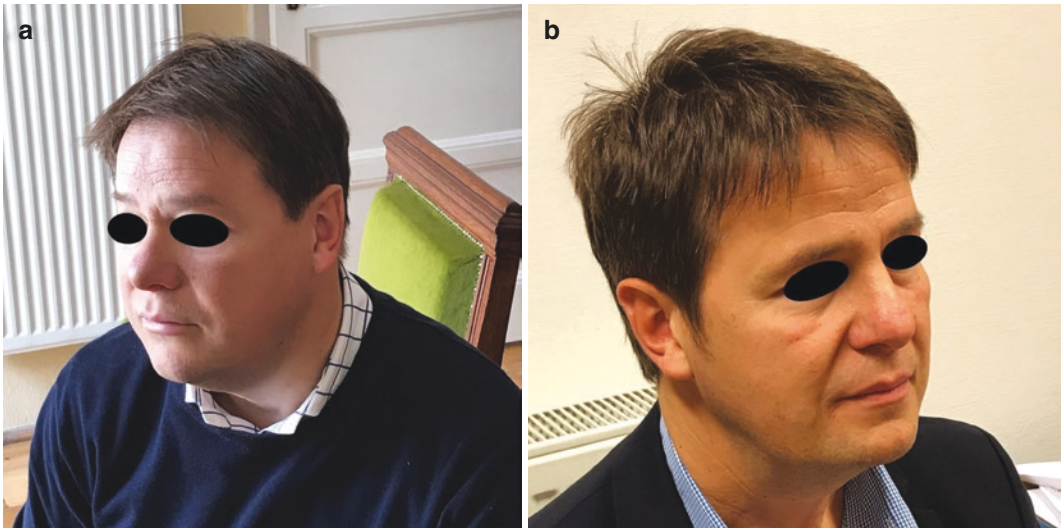

Fig. 11.2 Patient's face with overt hypothyroidism before **a** and after treatment **b**. Note the swollen facial appearance (puffiness), round shape, and periorbital edema before treatment. The lateral part of the eyebrow is scarce (Hertoghe sign). (Courtesy of Prof. Peter Igaz, 2nd Department of Internal Medicine, Semmelweis University, Budapest)

Table 11.2 Typical symptoms and signs of hypothyroidism

Fatigue	Muscle weakness
General slowing down	Increased need of sleep/ sleepiness
Weight gain	Cold intolerance
Dry skin, broken nails	Non-pitting edema (myxedema)
Swollen face	Hoarseness
Hair loss	Lateral fall out of eyebrow (Hertoghe sign)
Lack of interest	Bad mood, depression
Memory disturbance	Irregular menstruation cycle
Infertility	Abortion
Libido reduction	Impotence
Bradycardia	Hypertension[a]
Constipation	

[a]Blood pressure can be elevated due to increased total peripheral resistance; however normal, or reduced, blood pressure can also occur in hypothyroidism

Table 11.3 Laboratory results of the patient

Lab parameter	Result	Unit	Reference range
Free T4 (fT4)	8.17	pmol/L	9.00–23.20
TSH	55.238	mIU/L	0.350–4.940
Prolactin	41.02	ng/mL	1.39–24.20
aTPO	3062.83	IU/mL	<5.60
aTG	315.4	IU/mL	0–115

It is important to note that 10% of the female population is positive for aTPO, and not all of them have Hashimoto's thyroiditis. Positivity for aTPO without clinical symptoms is a predisposition for future thyroid disease. The prevalence of aTPO in a region is influenced by the iodine supply. Table 11.3 presents the hormone and aTPO findings of the patient.

General Laboratory Parameters

In overt hypothyroidism, elevated cholesterol, and CK (creatine kinase), moreover, normocytic anemia is often present. Decreased glomerular filtration rate (GFR) and sometimes slightly decreased serum sodium level are notable. All of these parameters are reversible after the correction of thyroid function.

Radiology Studies

Neck Ultrasound

Hashimoto's thyroiditis has typical ultrasound features. Typically, the thyroid is enlarged (total volume > 18 ml) with presence of marked hypoechoic micronodules with surrounding echogenic septations. Vascularization on color Doppler is often increased. Prominent reactive central lymph nodes in level VI are frequently seen (Fig. 11.3). In later stages of the disease, however, a small, firm, atrophic gland is often observed.

Is thyroid scintigraphy (^{99m}Technetium pertechnetate), CT, or MRI useful in the diagnosis of hypothyroidism?

None of these imaging modalities are useful or necessary for the diagnosis of hypothyroidism. Thyroid scintigraphy is indicated in primary thyroid diseases with low TSH values for the differentiation of hyperthyroidism.

What kinds of additional tests are needed?

Type 1 diabetes mellitus, atrophic gastritis, vitiligo, primary adrenal insufficiency, and celiac disease as part of autoimmune polyendocrine syndromes (mostly type 2, ▶ Chap. 31) have increased prevalence in patients with Hashimoto's thyroiditis.

In case of an autoimmune thyroiditis, screening for celiac disease is recommended. Other, organ-specific autoimmune diseases can be screened upon clinical suspicion.

Do we need fine needle aspiration cytology for diagnosis?

Just to ensure the diagnosis of Hashimoto's thyroiditis, fine needle aspiration cytology (FNAC) is not needed. If the typical ultrasound alteration is visible and there is a marked aTPO positivity, the cytology would not give any further useful information for diagnosis. In case of an unambiguous clinical picture (e.g., aTPO is negative but ultrasound is typical), an ultrasound-guided FNAC can be done

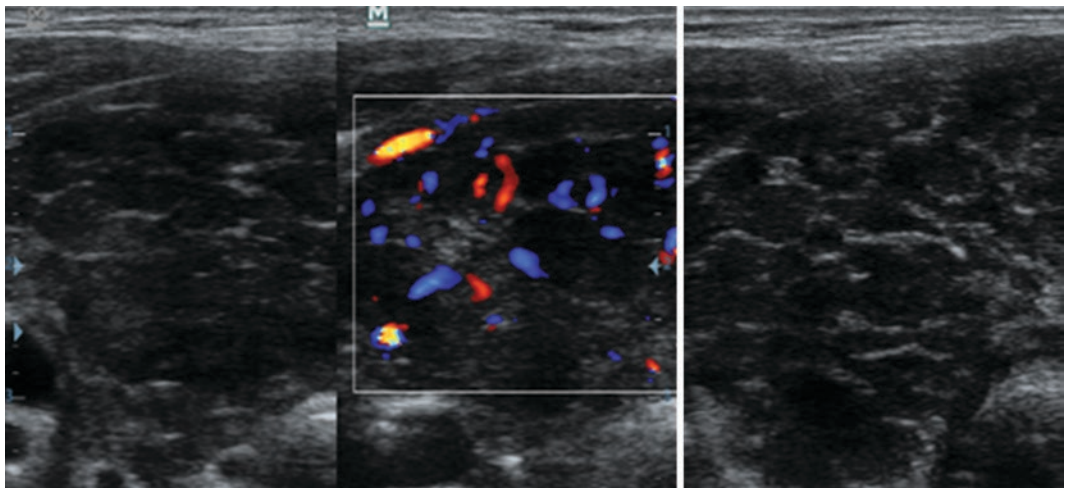

Fig. 11.3 Ultrasound imaging of the case: many hypoechoic microareas (2–4 mm) with surrounding echogenic septations, also called a giraffe pattern

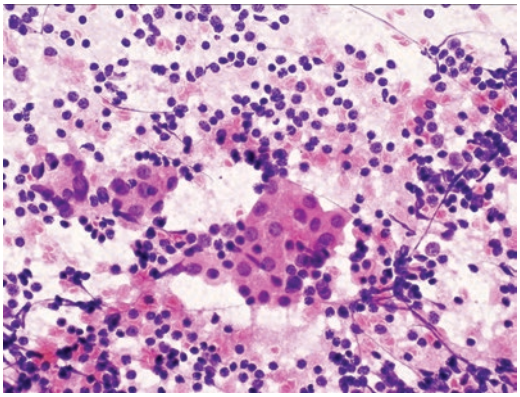

Fig. 11.4 Cytological appearance of Hashimoto's thyroiditis of FNA. (Courtesy of Eszter Székely, MD, 2nd Department of Pathology, Semmelweis University, Budapest)

from the hypoechoic structures of the gland that usually shows extreme lymphocytic infiltration, Hürthle cells/oncocytes with reduced colloid, or giant cells (Fig. 11.4). To further divide the thyroiditis into its subtypes (see below), occasionally FNAC can help. In nodular thyroid disease with a suspicion for malignancy, FNAC must be done.

Is it essential to differentiate the subtypes of Hashimoto's thyroiditis?

Hashimoto's thyroiditis is the group name of chronic lymphocytic thyroiditis. There are some subtypes of this thyroiditis. All subtypes can occur with dysfunction from subclinical to overt hypothyroidism and transient thyrotoxicosis. To differentiate the subtypes, the clinical picture and the ultrasound features or occasionally FNAC can help.

The following subtypes of Hashimoto's thyroiditis have been established:

- The most common is the classic variant with a strong female predominance (12:1) that is mostly diagnosed between 40 and 60 years of age. Patients can have normal thyroid functions at diagnosis, but hypothyroidism can also be observed.
- The fibrous variant is observed in less than 10% of cases and usually in women of 60–70 years of age (female-male ratio is about 10:1). Patients are usually hypothyroid at diagnosis. Severe fibrosis is a characteristic feature of this subtype.
- The most recently described very rare IgG4-related variant is associated with a rather rapid progress and subclinical hypothyroidism often despite levothyroxine substitution. The female-male ratio is only 3:1.

These first three forms are all characterized by fibrosis that is the most severe in the fibrous variant. Beside the IgG4-related variant, the fibrous variant is also related to IgG4. Riedel's thyroiditis (shortly discussed in the chapter on subacute thyroiditis (▶ Chap. 16)) is also an IgG4-related disease, but it extends over the thyroid capsule and infiltrates the surrounding neck structures.

- Juvenile thyroiditis is observed under 18 years of age, and patients can be both euthyroid and hypothyroid (subclinical or overt) or rarely hyperthyroid at presentation.
- Hashitoxicosis refers to a rare form characterized by immune-mediated thyrotoxicosis resembling Graves' disease that can last for several months (see later).
- Silent thyroiditis is most commonly observed after delivery, i.e., postpartum thyroiditis that can thus be categorized as a form of Hashimoto's thyroiditis (presented in detail in ▶ Chap. 21).

All these forms are characterized by hypoechogenicity on ultrasound, but nodular lesions are also seen in the fibrous variant.

Many cases are obvious (e.g., postpartum, juvenile) by the clinical presentation. In individual cases one needs to clarify the subtype of Hashimoto's thyroiditis, and FNAC can give further information.

What is the goal of the therapy?

There is no available therapeutic possibility that can prevent the irreversible destruction of the gland or restore the original tissue structure and function. The aim of the therapy is to restore the patient's normal condition, abolish his/her symptoms, and maintain the thyroid hormonal needs for long term.

What kind of therapeutic possibilities are available?

Although it is an autoimmune disease, there were many studies that failed to show any improvement of the gland's structure or function upon immunosuppressive therapy. Thus, the initiation of local or systematic corticosteroids (or any other immunosuppressive drugs) has no indication in the treatment of Hashimoto's thyroiditis (except of IgG4-related thyroiditis).

Hormone replacement therapy is the choice. According to international guidelines, levothyroxine (T_4) substitution is recommended. This substitution therapy maintains the patient's hormone needs with long-term safety. Since the deiodinase function is not disturbed in primary hypothyroidism, T_4 can be converted to T_3 in the peripheral tissues.

Other replacement therapy options as solely T_3 substitution or combined $T_4 + T_3$ drug or even desiccated thyroid extract are not recommended as first-line therapy. In very rare, selected cases, when levothyroxine therapy fails to adjust the hormone supply and/or the patient continues to report symptoms associated with hypothyroidism, one might try to launch these alternative replacement possibilities.

When should levothyroxine be taken?

The absorption of the T_4 drug in the intestine is sensitive. Levothyroxine should be taken early morning, after waking up, 30 minutes before breakfast/coffee or consuming juice, smoking, etc. An alternative option can be to take it 2–3 hours after the meal.

Is there any effect of additional micronutrients or vitamin supplementation?

In Hashimoto's thyroiditis, the supplementation of iodine might provoke intensification of the local inflammation in the thyroid, so it is to avoid. Since the initiation of the worldwide iodization program, the main sources of iodine in the Western diet are iodized salt used in processed food and products with naturally high iodine concentrations such as milk, dairy products, and seafood. Extra supplementation of iodine (multivitamins, algae) is not recommended.

Selenium is a micronutrient that has some favorable effects to decrease the aTPO level without apparent improvements in the clinical course of the disease. Moreover, the supplementation of selenium during pregnancy can reduce the risk of postpartum thyroiditis in women with aTPO positivity. Supplementation in organic form seems to be more effective (selenomethionine). The recommended daily dose is between 55 and 75 μg; however some experts advise to use a higher amount (up to 200 μg).

There are many studies that showed an association between low vitamin D status and the pathogenesis of autoimmune thyroid disease. However, very few good studies are available to evaluate the effect of vitamin D supplementation on the clinical course of Hashimoto's thyroiditis. The correction of vitamin D deficiency is recommended.

Moreover, there is no convincing scientific evidence about the beneficial effect of gluten- or lactose-free diet.

What are the main treatment and follow-up aspects?

- To evaluate the success of the substitution, one needs to check the patient's condition, whether the symptoms diminished or abolished. For laboratory test in case of primary hypothyroidism, TSH alone is enough.

- The target TSH level should be set individually. The TSH target in young patients should be around 2,5 mIU/L and also in those women who plan pregnancy. The TSH in middle-aged people should be in the reference range, while in elderly patients, the TSH can be adjusted to be a little bit higher, but less than 8–10 mIU/L.

- Controlling the level of aTPO has no additive value. Upon levothyroxine supplementation, controlling of free hormones does not have any additional information, since levothyroxine is measured in the fT_4 level.

- After initiating or modifying the levothyroxine supplementation, at least 4 weeks should be waited for the next TSH control. If the TSH target level is achieved and the patient is in a stable condition, the control of TSH is recommended every 6–12 months.

Is there a risk for malignancy in Hashimoto's thyroiditis?

- Patients with Hashimoto's thyroiditis have an increased risk for papillary thyroid cancer, and rarely intrathyroidal lymphoma can appear. Therefore, ultrasound scan every 2–3 years is recommended. If a nodule is detected, it should be evaluated for cancer risk according to the actual guidelines (TI-RADS, size, ultrasound features, FNAC).

Should everybody be treated?

- Every patient with overt hypothyroidism should be treated!

- Patients, who have aTPO positivity and/or ultrasound features for thyroiditis but no functional deviation of the thyroid, can be observed. One might advise the supplementation of selenium in these cases.

- Decision for treatment in patients with subclinical hypothyroidism can be made individually. Elderly (over 70 years) patients with TSH level under 8–10 mIU/L without any pronounced symptoms can also be observed.

- Patients under 70 years with subclinical hypothyroidism without any cardiovascular disease can be checked without launching medication. However, in patients (under 70 years) with cardiovascular disease, the restoration of the thyroid function can give additional value, since subclinical hypothyroidism under 70 years increases the risk for cardiovascular disease.

- Young female patients with subclinical dysfunction planning pregnancy should be also treated, where the goal TSH level is around 2,5–3 mIU/L.

How should the therapy with levothyroxine be initiated?

- The initiation of levothyroxine supplementation in many cases should be gradual. Most of overt hypothyroidism lasts for many weeks and months before diagnosis, so the body has adapted to the low T_4 circumstances (receptor upregulation). If a huge amount of T_4 would be given to a patient with overt hypothyroidism, it can deteriorate his clinical state. Starting with 50 µg/day, which can be increased after a week or two by 25 or 50 µg, is recommended. The overall daily levothyroxine needs is around 1,5 µg/bodyweight. After thyroidectomy the total amount of levothyroxine needs can be substituted. In elderly patients with severe cardiovascular diseases, tiny amounts of levothyroxine, such as 12,5 or 25 µg starting dose/day, are recommended.

Is dopamine agonist treatment due to the hyperprolactinemia warranted?

Dopamine agonist therapy is not needed, if the reason of hyperprolactinemia is due to primary hypothyroidism. Prolactin will spontaneously reduce a few weeks after initiation of levothyroxine treatment.

Can Hashimoto's thyroiditis begin with hyperthyroidism?

In several cases the active immunological process (T-cell-mediated cell destruction, antibody-mediated inflammation) destroys the structure of the thyroid gland, and the preformed thyroid hormones stored in the colloid unregulated flow out in the circulation. Such an uncontrolled increase of blood T_4 concentration can induce a transient thyrotoxicosis with modest clinical symptoms. This kind of thyrotoxicosis lasts for a few weeks or months and then turns into subclinical or overt hypothyroidism. Since it is a destructive thyrotoxicosis, starting a thyrostatic medication is not recommended, and a symptom-orientated therapy (usually beta-blocker) is enough. Thyroid scintigraphy in such a destructive thyroiditis shows no uptake.

On the other hand, hashitoxicosis, a rare form of Hashimoto's thyroiditis, is an immune-mediated thyrotoxicosis that is very difficult or impossible to differentiate from Graves' disease (▶ Chap. 12). In contrast with the other forms of Hashimoto's thyroiditis, isotope uptake on thyroid scintigraphy is increased in this case.

What is Hashimoto encephalopathy?

It is a rare type of corticosteroid-responsive encephalopathy associated with positive antithyroid antibodies. Hashimoto encephalopathy is an exclusion diagnosis, if no other reason can be found in patients with positive aTPO and/or thyroiditis. Studies revealed a potential autoantibody, anti-α-enolase, that is associated with the disease. There is no direct evidence linking thyroid dysfunction or antithyroid antibodies with clinical features of this encephalopathy.

What is the most severe complication of hypothyroidism?

Very rarely, hypothyroid coma (or myxedema coma) can develop in untreated patients with hypothyroidism, most often following a precipitating event (e.g., infection, gastrointestinal hemorrhage, burns, trauma, surgical intervention, drugs (narcotics, tranquilizers, amiodarone, lithium carbonate)). Hypothyroid coma is associated with an altered mental status (coma in the most severe cases), hypothermia (core temperature usually <35.5 °C), severe bradycardia, meteorism, and even paralytic ileus. Hypoventilation and hypoglycemia are also often present. Diastolic blood pressure may be increased in the beginning (due to increased peripheral vascular resistance), but later hypotension can develop. In severe hypothyroidism, pericardial effusion can develop that might even lead to pericardial tamponade. Low voltage on ECG can be a sign of pericardial fluid. If it is not recognized and thus left untreated, the mortality of hypothyroid coma is high.

The mainstay of treatment is levothyroxine administered mostly via the intravenous route (100–500 μg i.v. on the first day and then 75–100 μg daily till oral administration is possible). Parenteral hydrocortisone (e.g., 3 × 100 mg/24 h in infusions) is also needed until concomitant adrenal insufficiency is ruled out, since hypothyroidism can be associated with adrenal insufficiency in the context of autoimmune polyendocrine syndrome type 2. (Secondary hypothyroidism can also be associated with secondary adrenal insufficiency due to hypopituitarism (▶ Chap. 6).) Antibiotics can also be given.

What would you think of a thyroid hormone constellation involving low or normal TSH and low T4 and T3 levels in a critically ill patient?

In critically ill patients (e.g., treated in intensive care units) of miscellaneous causes (starvation, renal or liver insufficiency, heart failure, infections), such a constellation can occur without an underlying disease of the thyroid. This syndrome is called non-thyroidal illness (previously termed as euthyroid sick syndrome or low T3 (or low T3–T4) syndrome) and is in part associated with the increased metabolism of thyroid hormones resulting in an increased level of inactive reverse T3 (rT3). However, the hormone alterations can be quite variable. Drugs used in intensive care (e.g., high-dose glucocorticoids and pressor amines (dopamine, dobutamine)) can affect the thyroid; moreover, they can make the interpretation of thyroid hormone results difficult. Non-thyroidal illness usually does not need specific treatment, and there is no evidence that thyroid hormone replacement would be beneficial. The syndrome might even represent an adaptive mechanism protecting against catabolic processes. The hormonal constellation actually corresponds to that of secondary hypothyroidism, and novel data show that a transient secondary hypothyroidism might also play a role. It is advised that thyroid function tests should only be performed in those cases of critically ill patients, where the suspicion for thyroid disease is strong.

Tips

The reader is advised to read the chapters on thyroid nodule and multinodular goiter (▶ Chap. 15) and Graves' disease (▶ Chap. 12) and the chapter on Addison's disease and autoimmune polyendocrine syndrome type 2 (▶ Chap. 31). Other forms of thyroiditis are discussed in ▶ Chaps. 16 and 17 (subacute thyroiditis and amiodarone-induced thyroiditis).

Take-Home Messages

- Hypothyroidism is a common endocrine disease.
- In case of primary thyroid insufficiency, TSH will be increased, and fT4 can be still in the reference range (subclinical form) or decreased (overt form).
- The most common etiology is the chronic lymphocytic thyroiditis, called Hashimoto's thyroiditis.
- The hallmarks of Hashimoto's thyroiditis are the increased serum aTPO and the typical ultrasound features of the thyroid.
- Overt hypothyroidism is needed to treat, whereas decision for treatment in case of subclinical form should be made individually.
- The choice of treatment is levothyroxine monotherapy for substitution.

Case Presentation Summary

The female patient has a chronic lymphocytic thyroiditis, since aTPO is markedly positive and ultrasound features show diffuse hypoechogenicity. Overt hypothyroidism is detected, so the initiation of levothyroxine is essential. Dopamine agonist therapy due to hyperprolactinemia is not required, and prolactin should be controlled after euthyroidism is achieved.

The starting dose of levothyroxine can be 50 μg/day for a week and then change to 75 μg/day. After 4–6 weeks of medication, TSH should be controlled. If TSH is still above the target level (in this case around 2.5–3 mIU/L), further dose escalation is required.

Although, hypertension is revealed, no antihypertensive medication is needed at the beginning, since the improvement of thyroid function can improve blood pressure.

All the symptoms mentioned by the patients can disappear in a few weeks/months upon levothyroxine supplementation.

Suggested Reading

1. Adler SM, Burman KD. Chapter 17: Chronic thyroiditis. In: Clinical management of thyroid disease; 2009. p. 241–53. https://doi.org/10.1016/B978-1-4160-4745-2.00017-1.
2. Biondi B, Cappola AR, Cooper DS. Subclinical hypothyroidism: a review. JAMA. 2019;322(2):153–60. https://doi.org/10.1001/jama.2019.9052.
3. Brent GA, Davies TF. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors. Hypothyroidism and thyroiditis in Williams textbook of endocrinology. 12th ed. Philadelphia: Elsevier; 2011. p. 407–34, ISBN:978-1-4377-0324-5.
4. Caturegli P, De Remigis A, Rose NR. Hashimoto thyroiditis: clinical and diagnostic criteria. Autoimmun Rev. 2014;13(4–5):391–7. PMID: 24434360. https://doi.org/10.1016/j.autrev.2014.01.007.
5. Duntas LH. The role of iodine and selenium in autoimmune thyroiditis. Horm Metab Res. 2015;47(10):702–10. https://doi.org/10.1055/s-0035-1559631.
6. Hiromatsu Y, Satoh H, Amino N. Hashimoto thyroiditis: history and future outlook. Hormones (Athens). 2013;12(1):12–8. https://doi.org/10.1007/BF03401282.
7. Kottahachchi D, Topliss DJ. Immunoglobulin G4-related thyroid diseases. Eur Thyroid J. 2016;5(4):231–9. https://doi.org/10.1159/000452623.
8. Leslie J, De Groot J, Jameson L. Endocrinology adult and pediatric: the thyroid gland E-Book. Philadelphia: Elsevier Health Sciences; 2013. p. e242–54, ISBN 032322153X.
9. Maiden MJ, Torpy DJ. Thyroid hormones in critical illness. Crit Care Clin. 2019;35(2):375–88. https://doi.org/10.1016/j.ccc.2018.11.012.
10. Pearce EN, Farwell AP, Braverman LE. Thyroiditis. New Engl J Med. 2003;348(26):2646–55. https://doi.org/10.1056/NEJMra021194.
11. Ragusa F, Fallahi P, Elia G, Gonnella D, Paparo SR, Giusti C, Churilov LP, Ferrari SM, Antonelli A. Hashimotos' thyroiditis: epidemiology, pathogenesis, clinic and therapy. Best Parct Res Clin Endocinol Metab. 2019;33(6):11367. https://doi.org/10.1016/j.beem.2019.101367.
12. Wall CR. Myxedema coma: diagnosis and treatment. Am Fam Physician. 2000;62(11):2485–90.
13. Zhou JY, Xu B, Lopes J, Blamoun J, Li L. Hashimoto encephalopathy: literature review. Acta Neurol Scand. 2017;135(3):285–90. https://doi.org/10.1111/ane.12618.

Graves' Disease and Hyperthyroidism

Peter Reismann

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_12

Opening

In this chapter, one of the most interesting thyroid disorders will be discussed. Graves' disease is an autoimmune thyroiditis with a bright spectrum of clinical appearance. Typical manifestations include thyrotoxicosis/hyperthyroidism, goiter, and ophthalmopathy (endocrine orbitopathy: EO) in 25% of patients. Having read this chapter, the reader will be able to distinguish the potential causes of thyrotoxicosis and able to manage it.

Definition of the Disease

Graves's disease has alternative names: Morbus Basedow or Graves-Basedow disease. It is an organ-specific autoimmune thyroiditis, but in 25% it can come along with extrathyroidal, mainly eye manifestations. The disease evokes functional disturbances, i.e., primary hyperthyroidism. In areas with sufficient iodine intake, Graves's disease is the most common cause of thyrotoxicosis with a prevalence of 0.5%. There is a female dominance, and young and middle-age women are typically affected. Genetic and environmental factors (smoking, stress, heavy weight loss, pregnancy, iodine intake excess) contribute together to the development of disease. As an autoimmune disease, loss of immune tolerance and the appearance of antibodies against the TSH receptor (TRAb: TSH receptor antibodies) are responsible for the hyperthyroidism. The binding of TRAb to the TSH receptor on the surface of thyroid follicular cells leads to a continuous and uncontrolled stimulation of hormone synthesis and release of T_4 (L-thyroxine) and/or T_3 (triiodothyronine) into the blood stream. Furthermore, the continuous activation of the TSH receptor induces hypertrophy of the tissue, resulting in goiter as the clinical consequence.

In contrast to primary hyperthyroidism that is caused by a disease of the thyroid gland, secondary hyperthyroidism is caused by the overproduction of TSH by a pituitary adenoma. TSH-secreting adenoma, however, is very rare with an incidence of 1–2/million/year.

Case Presentation

A 25-year-old lady was admitted to the endocrine outpatient clinic with the following symptoms lasting for 2 months: 5 kg unintentional weight loss, fatigue, sleep disturbances, tremor in the hands, increased appetite, irritability, increased stool frequency, hair loss, palpitation, excess sweating, epiphora (excessive tearing), and pain and redness in eyes. Her previous history was unremarkable, but her family history was positive for thyroid disease (mother and grandmother). The patient did not take any medication but took multivitamin tablets on a daily basis. Her menstrual cycle became irregular in the last months. She was never pregnant but planned it in the upcoming years.

Physical examination revealed a skinny young, female patient with a BMI of 20 kg/m^2 (body weight, 55 kg; height, 165 cm). Her skin was wet and warm. Her hands showed a fine tremor. Blood pressure was 164/78 mmHg with a regular pulse of 124/min. There was a quiet systolic heart murmur over the chest and also a quiet murmur over the thyroid. Increased bowel movements were heard. The thyroid was enlarged, but no nodule was palpable. By examining her eyes, eyelid retraction, exophthalmos, and chemosis were detectable. The patient was restless but orientated with no focal neurological symptoms.

Which pieces of information are important regarding thyroid dysfunction?

Female relatives had thyroid disease, which is a common hallmark. The patient had the typical symptoms of hyperthyroidism as weight loss, irregular menses, increased stool frequency, hair loss, restless-irritability, tremor in hands, goiter, accelerated blood circulation, and signs of endocrine orbitopathy. Table 12.1 presents the typical symptoms and signs in Graves' disease.

The typical features for Graves' disease had a classical phrase – "The Merseburg triad": palpitation, goiter, and exophthalmos (endocrine orbitopathy). The name is related to the German physician, Carl Adolph von Basedow, who worked in Merseburg and was one of the first to describe the syndrome. Robert James Graves, a physician in Dublin, and Hillier Parry from England had similar cases reported earlier.

Additional important pieces of information can be the ingredients of multivitamin that was taken by the patients. Many multivitamins contain iodine. Excess intake of iodine can be a trigger factor for patients having risk for autoimmune thyroiditis.

Physical examination revealed heart murmur over the thyroid. Hyperthyroidism increases the workload of the heart, and tachycardia generates a functional heart murmur. Furthermore, systolic hypertension with tachycardia is typical for hyperthyroidism. Murmur over the thyroid originated from the increased blood flow in the thyroid.

Eye symptoms are discussed in "ophthalmological examination" part in more detail and in the chapter "Endocrine Orbitopathy" (▶ Chap. 14).

Table 12.1 Physical signs and symptoms of Graves' disease

Symptoms	Physical signs
Weight loss	Tachycardia, atrial fibrillation
Increased stool frequency	Systolic hypertension
Thirst and polyuria	Cardiac failure
Heat intolerance, increased sweating	Warm, wet skin, hair loss
Menstrual disturbances in women	Palmar erythema, onycholysis
Tiredness, fatigue	Diffuse goiter – thyroid bruit
Anxiety, sleep disturbances, nervousness	Exophthalmos – proptosis (endocrine orbitopathy)
Eye symptoms	Periorbital edema, chemosis
Palpitation	Acropachy
Tremor	Fine tremor, hyperreflexia
	Pretibial myxedema

What are the essential initial diagnostic steps?

Laboratory Examinations

In general, screening for *TSH* alone is enough to evaluate thyroid functioning. Many laboratories set an automatic process, and if TSH turns out to be under the reference range, fT_4 and fT_3 will be automatically measured.

If TSH is suppressed (<0.1 mIU/L) and the free thyroid hormones (fT_4 and/or fT_3) are above their reference range, that is *overt primary hyperthyroidism*. The terms hyperthyroidism and thyrotoxicosis are most often used synonymously. In very strict terminology, however, hyperthyroidism refers to thyroid hormone overproduction, whereas thyrotoxicosis comprises the clinical symptoms and manifestations.

In contrast, in the very rare secondary hyperthyroidism caused by a TSH-producing pituitary adenoma, TSH is normal or elevated, and free thyroid hormones are high, as well.

What is subclinical primary hyperthyroidism?

If TSH is under its reference range, but the peripheral hormones are still in their reference range, this situation is called subclinical primary hyperthyroidism. According to the European guideline from ETA (European Thyroid Association), subclinical hyperthyroidism has two grades. Grade 1 has low but detectable TSH, meaning biochemically a TSH between 0.1 and 0.39 mIU/L, whereas Grade 2 has suppressed serum TSH <0.1 mIU/L.

Nota bene: In case of low TSH with normal peripheral thyroid hormones, please evaluate the possibility of secondary hypothyroidism in the context of hypopituitarism (read ► Chap. 6).

12

What can be the cause of hyperthyroidism?

If primary hyperthyroidism is detected, the following possible causes should be figured out:

- Graves' disease
- Toxic goiter (single or multinodular)
- Initial phase of Hashimoto thyroiditis
- Initial phase of other forms of thyroiditis (postpartum/de Quervain (subacute))
- Drug-induced hyperthyroidism (e.g., amiodarone)
- Excess iodine (vitamin, algae, CT contrast agent)
- Overdose of levothyroxine (factitious thyrotoxicosis)
- Struma ovarii (thyroid tissue in the ovary in a form of a monodermal teratoma, usually associated with a mild hyperthyroidism)
- Advanced clinical stage in metastatic differentiated thyroid cancer
- First trimester of pregnancy (hCG-induced form)

What are the main differences between the symptoms of Graves' disease and toxic goiter?

Graves' disease and toxic goiter (see ► Chap. 15 on thyroid nodule and multinodular goiter, as well) represent the main causes of primary hyperthyroidism. The symptoms related to the metabolic actions of thyroid hormone overproduction are the same; the only major difference is the lack of autoimmune-related phenomena (most importantly endocrine orbitopathy) in toxic goiter.

What kind of examinations can be used for differential diagnosis?

Since Graves' disease is an autoimmune form of hyperthyroidism, detection of autoimmune markers is helpful. Beside laboratory investigations, radiology studies are also needed.

What are the autoimmune markers of Graves' disease?

Measurement of *thyrotropin (TSH) receptor autoantibodies* (TRAb) has a 99% sensitivity and specificity for Graves's diseases. *Thyroid peroxidase autoantibody* (aTPO) can be also positive in many cases, which can occasionally make the differential diagnosis between initial phase of Hashimoto thyroiditis and Graves's diseases difficult. However, high concentration of TRAb and a typical clinical appearance favor the diagnosis of Graves' disease.

There is no need to measure thyroglobulin or its antibody.

TRAb is a mixture of blocking and stimulating autoantibodies for the TSH recep-

tor. It would be helpful, if we could distinguish between the blocking and stimulating antibodies, but it is not yet available in the clinical settings.

In other forms of hyperthyroidism, especially in toxic nodular goiter (that is more common in iodine-deficient regions), antibody detection is negative.

What are the features of general laboratory parameters?

Mild low white blood cell concentration is common in untreated Graves' disease; this is the classical Kocher blood picture: leukopenia, neutropenia (relative hypopolynucleosis), and relative lymphocytosis. Alkaline phosphate (ALP) can be higher that is not a sign of hepatic injury, but rather a consequence of the accelerated bone turnover in Graves' disease. Hyperglycemia can be present.

Is thyroid scintigraphy (^{99m}Technetium pertechnetate) useful in the diagnosis of hyperthyroidism?

Yes, the indication of thyroid scintigraphy is the differential diagnosis of primary hyperthyroidism. In Graves' disease, homogeneously increased uptake is detectable (Fig. 12.1). In toxic nodular goiter, there is a patchy uptake or single "hot" nodule surrounded with low uptake areas (see ▶ Chap. 15/▶ Fig. 15.5 on thyroid nodule and multinodular goiter, as well). In other forms of hyperthyroidism, low or no uptake is detectable (e.g., different forms thyroiditis, exogenous levothyroxine (factitious thyrotoxicosis), ectopic thyroid tissue).

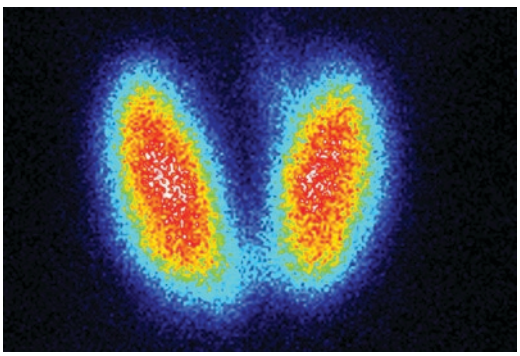

Fig. 12.1 Homogenous, increased uptake of the thyroid on ^{99m}technetium pertechnetate thyroid scintigraphy: Graves' disease. (With permission of the Chair of Nuclear Medicine, Semmelweis University)

What is the role of the neck ultrasound in hyperthyroidism?

Ultrasound of the thyroid can be helpful, but alone it does not have the sensitive power for diagnosis. The thyroid gland is often enlarged (female >18 ml, male >25 ml), and the echotexture is mainly heterogeneous. The most typical feature is the diffuse hypervascularity; one might call it "thyroid inferno" pattern on color Doppler. Figure 12.2 shows typical ultrasound pictures of Graves' disease.

Alongside the typical morphological features of Graves' disease, nodules can be also detected in thyroid ultrasound. Then the question arises if whether the nodule is functional active, acting as a toxic nodule or not. In such cases the scintigraphy can give the answer. Exact collation of the thyroid ultrasound and scan pictures can rule out the functional activity of the nodule.

Do we need other additional examinations for diagnosis?

For the diagnosis of Graves' disease, either TRAb or thyroid scintigraphy is enough. If TRAb is markedly positive, there is no need for scintigraphy. Inversely, if scintigraphy shows a homogenous increase uptake, TRAb is not necessary for diagnosis.

Do we need to perform fine needle aspiration cytology from Graves' thyroiditis?

Generally, FNAC is not needed for diagnosis. However, if a nodule is detected in Graves' disease, the evaluation for malignancy should be made. There is a higher

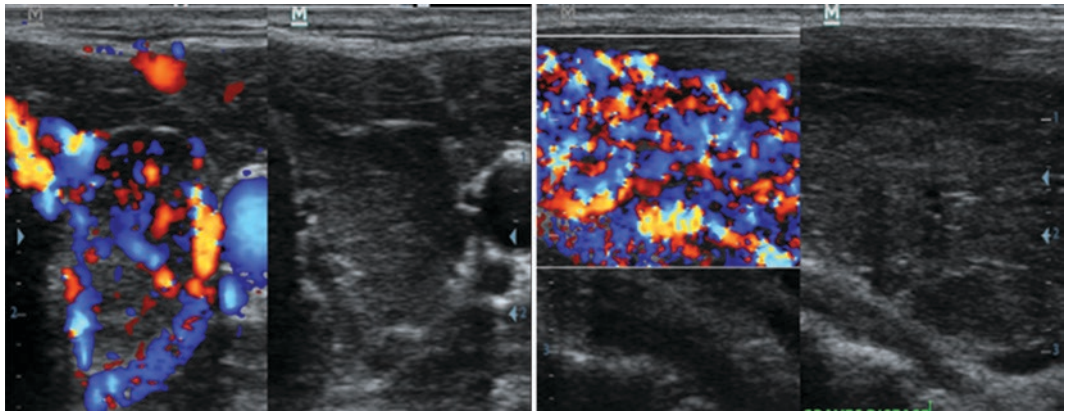

Fig. 12.2 Ultrasound pictures of Graves' disease: the so called thyroid inferno is seen. The main echotexture is mostly decreased, inhomogeneous with extremely increased diffuse hypervascularity on color Doppler

risk of differentiated thyroid cancer in nodules of Graves' disease. In suspicious cases, fine needle biopsy is needed for cytology.

What other examinations are needed after confirmation of Graves' disease?

Ophthalmological Examination

Graves' disease has extrathyroidal manifestations including the endocrine orbitopathy (EO, synonyms: GO (Graves' ophtalmopathy), thyroid eye disease) that is observed in up to 30% of patients (detailed in ▶ Chap. 14).

Orbital involvement is a consequence of the autoimmune process in Graves' disease. The clinical presentation of ophthalmopathy ranges from mild to sight-threatening severity. Risk factors for the EO are smoking, rapid changing of thyroid function (fluctual hyper-hypothyroidism), and mechanical irritation (sunshine, wind). In the majority of patients, the eye problems develop in parallel with the onset of thyroid disease.

TRAb evokes an inflammation of the extraocular muscles and orbital adipose, connective tissue. The muscle and adipose tissue are expanded. The increase in volume of the orbital adipose and muscle tissue influences the severity of the orbitopathy. Muscle dysfunction (mostly the inferior rectus muscle) leads to diplopia and limitation of eye movements. In severe cases, the intraorbital pressure can injure the optical nerve and the blood supply of the orbita.

In mild disease, patients have eyelid retraction, mostly upper eyelid retraction (Dalrymple's sign). Graefe's sign is the lagging of the upper eyelid on downward rotation of the eye, whereas lagophthalmos is the incapacity of closing the eyelids while incomplete and infrequent blinking is called Stellwag's sign. Möbius sign is the lack of convergence. These are the classical eye signs of Graves' disease that are reversible, but the symptoms of endocrine orbitopathy as detailed in ▶ Chap. 14 are more severe and often irreversible.

Due to eyelid retraction and lagophthalmos, the cornea becomes dry and presents with chemosis, epithelial erosions, and conjunctivitis. Symptoms include irritation, photophobia, tearing, and blurred vision.

In moderately active disease, muscle dysfunctions appear with diplopia. The intraocular pressure can be increased. In severe forms of EO, progressive exophthalmos and myopathy restrict eye movements, and the optic nerve can be compressed. The

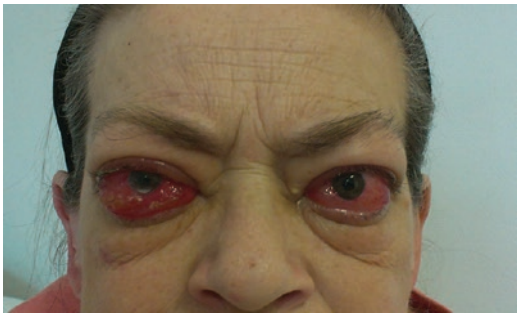

Fig. 12.3 A severe form of Graves' endocrine orbitopathy with chemosis (extensive conjunctival swelling and edema)

clinical appearance can be the loss of visual acuity, visual field defect, or total visual loss (Fig. 12.3).

In case of eye symptoms or signs of EO, a thorough ophthalmological examination and regular follow-up are warranted. ▶ Chapter 14 is dedicated to endocrine orbitopathy in detail.

What kinds of skin alterations can be seen in Graves' disease?

In very rare cases, thyroid dermopathy can be detected. Usually it comes along with severe orbitopathy. The typical localization of dermopathy is the pretibial region (pretibial myxedema, a non-pitting edema similar to that observed in hypothyroidism). Acropachy is clubbing of the fingers and toes. In such cases dermatological examination is advised.

What about cardiac alterations?

Severe hyperthyroidism provokes systolic hypertension, tachycardia, and in elderly patients often atrial fibrillation. Congestive cardiac failure can be a consequence of thyrotoxicosis. Therefore, a cardiac examination and regular follow-up with ECG and echocardiography are often needed.

What kinds of additional tests are needed?

Type 1 diabetes mellitus, atrophic gastritis, vitiligo, primary adrenal insufficiency, and celiac disease as part of autoimmune polyendocrine syndromes (mostly type 2, ▶ Chap. 31) have increased prevalence in patients with Graves' thyroiditis.

In case of an autoimmune thyroiditis, screening for celiac disease is recommended. Other organ-specific autoimmune disease can be screened upon clinical suspicion.

What is Marine-Lenhart syndrome?

Marine-Lenhart syndrome is the coexistence of Graves' disease with a functional active toxic nodule of the thyroid. Primary hyperthyroidism has then two sources at the same time.

What is the goal of the therapy?

Spontaneous remission occurs in a small proportion of patients, and long-term remission is also known. Long-term untreated hyperthyroidism impairs heart function, provokes osteoporosis, and can reduce life expectancy. Therefore, therapy of Graves' hyperthyroidism is absolutely recommended.

The aim of the therapy is to restore the patient's normal condition, abolish his/her symptoms, and reach and maintain euthyroid state.

If the patient smokes, it is essential to give it up.

What kinds of therapeutic possibilities are available?

There are several therapeutic options available to treat Graves' hyperthyroidism. Medical therapy consists antithyroid drugs, beta-blockers, selenium, and in selected cases lithium carbonate. Ablative therapy possibilities are the radioiodine and near-total thyroidectomy.

In Europe, the first-line treatment is the antithyroid drug therapy for 12–18 months.

Available drugs are methimazole (thiamazole), propylthiouracyl (PTU), and carbimazole. These drugs inhibit thyroid peroxidase function, thus blocking thyroid hormone production. As a first choice, methimazole/carbimazole is preferred in Europe. The goal of the antithyroid drug treatment is to restore and maintain the euthyroid state. In the beginning of the therapy, higher doses are often needed (methimazole 30–60 mg/day, propylthiouracil 300–400 mg/day), and later on, the daily dose can be reduced. In the first months of treatment, the concentrations of free hormones decrease, but TSH can be longer suppressed. There is an intention to maintain the free hormone level in their upper range with no clinical symptoms. After a while, TSH starts to increase. In case of moderate or severe ophthalmopathy, it is recommended to avoid the hypothyroid function or waving between hyper- and hypothyroid state. The dose reduction of antithyroid drug is an easily feasible method. Previously the "block and replace" method was also frequently used. In this treatment algorithm, the higher dose of antithyroid drug remains unchanged, but in the presence of hypothyroid hormone levels, levothyroxine was initiated. The combined therapy with antithyroid drug and levothyroxine is nowadays rarely used, and it is contraindicated in pregnancy.

- Long-term remission occurs in 30–40% of patients after 12–18 months of medical therapy. If Graves' disease recurs, the efficacy of repeated medical treatment is as low as 15–20%.

- Additional therapy with lithium carbonate has a minor role in the treatment, and it is given mostly in cases if antithyroid drugs are contraindicated due to severe side effects.

- Selenium might reduce the risk of EO.

- The nonselective beta-blocker propranolol reduces the tachycardia and on the other hand inhibits the peripheral conversion of T_4 to T_3. It is therefore especially useful in the beginning of symptoms. Anxiolytic drugs in low doses can also be given.

What kinds of side effects require attention in medical treatment?

- Antithyroid drugs have almost the same side effect profile. Granulocytopenia can be severe, and it presents in 0.2–0.3% of patients mainly in the first 3 months of treatment. Hepatotoxicity frequency is less than 0.1%, and ANCA-associated vasculitis is also a rare consequence of the therapy. Allergically skin reaction is also known.

- In case of a severe side effect associated with an antithyroid drug treatment, switching to another is not recommended.

- Regular checkup of blood count or liver function has no additive value according to available consensus opinion but can be occasionally checked in the beginning of the therapy. It is important to educate the patients of the signs and symptoms of agranulocytosis (fever, fatigue, sore throat, mouth ulceration, bleeding gums) and to stop the drug and seek urgent medical advice with these symptoms.

- Methimazole/carbimazole should be taken once a day (independently of the required daily dose), whereas propylthiouracil should be divided into three times a day!

What are the indications of ablative therapy?

- Ablative treatment consists of radioiodine (^{131}I) or surgical thyroidectomy. The goal of the ablative therapy is to permanently eliminate thyroid hyperfunction.

- Radioiodine cumulates in thyroid cells, and the radiation irreversibly destroys the thyroid tissue. The adequate surgical intervention nowadays is the near-total thyroidectomy in case of Graves' disease.

Previously, subtotal thyroidectomy was performed, but the recurrence of hyperthyroidism was high.

The consequence of ablative therapy is hypothyroidism in 80% of radioiodine and almost 100% after thyroidectomy. After successful ablative treatment, levothyroxine should be given lifelong for patients presenting with overt hypothyroidism.

The indications for ablative treatment are presented in ▶ Box 12.1.

Box 12.1 Indications for Ablative Treatment in Graves' Disease

- If severe side effect occurred during antithyroid drug treatment
- In case of recurrent Graves' disease after 12–18 months of antithyroid drug treatment
- If the patient does not want to take the antithyroid drug
- If medical treatment fails to restore euthyroid state

Which ablative therapy option should be chosen?

Physicians need to explain the benefits and risks of both ablative treatments for their patients.

Surgical removal of the thyroid is recommended in large goiter, multinodular goiter, for women wishing to be pregnant shortly after therapy, and for those who fear the radiation exposure. Patients with moderate or severe form of endocrine orbitopathy have better ocular outcome after thyroidectomy.

Before surgery, the restoration of thyroid function with antithyroid drugs is needed. Subclinical hyperthyroidism or euthyroid state is optimal for thyroidectomy. In many centers, preoperative treatment with inorganic iodine is a practice to decrease the thyroid blood flow, vascularity, and intraoperative bleeding.

Radioiodine treatment is an elegant form of ablative treatment. In North America, radioiodine treatment remains the first-line option for Graves' disease. The effect of radioiodine treatment is detectable after a few weeks. For successful treatment, patients need to have high iodine uptake capacity, which requires the termination of antithyroid drug treatment 7–10 days before therapy. Two options are available for treatment. Many clinicians use fixed doses of ^{131}I, whereas others calculate the needed activity before treatment. Radioiodine is not associated with increased risk of cancer, but recent studies question this statement. Radioiodine can provoke or worsen the endocrine orbitopathy. In mild or moderate cases, pretreatment with corticosteroid drug is advisable. After ablation of the thyroid, the function should be regularly monitored, and if hypothyroidism develops, levothyroxine substitution is required.

What are the special considerations in the treatment of pregnant women?

Pregnancy softens the natural course of Graves' disease, and signs and symptoms often improve. The background of this natural amelioration is the change in the immunological response. On the other hand, after delivery (postpartum), a rebound of the immune system can lead to the exacerbation of Graves' disease.

If hyperthyroidism is detected in a pregnant woman, beside the known causes mentioned above, another differential diagnostic cause should be evaluated: i.e., gestational transient thyrotoxicosis (most often observed between the 6th and 15th weeks of pregnancy). It is the consequence of elevated hCG (human chorionic gonadotropin) concentration in the blood. hCG can bind to the TSH receptor and acts as thyrotropin.

The severe form of gestational thyrotoxicosis is called hyperemesis gravidarum. The symptoms spontaneously resolve as serum concentration of hCG decreases.

- Patients with Graves' disease wishing to be pregnant should stabilize the thyroid function before conception. If medical treatment is needed, propylthiouracil is the choice in the first trimester. In the second or third trimester, both methimazole and propylthiouracil can be given. The target value of free hormones should be in their upper normal range. Hypothyroidism should be avoided.

- The usage of "block and replace" therapy is absolutely contraindicated in pregnancy.

- Radioiodine therapy and diagnostic scintigraphy are also prohibited during pregnancy.

- An additional guideline recommendation is that pregnancy should be kept off for 6–12 months after radioiodine therapy. More details on thyroid diseases in pregnancy are presented in ► Chap. 21.

What are the indications for treatment in subclinical hyperthyroidism and how treatment should be performed?

- The treatment of subclinical hyperthyroidism should be evaluated individually. According to the recent ETA guideline, treatment of Grade 2 subclinical hyperthyroidism (TSH < 0.1 mIU/L) is recommended in patients over 65 years. Treatment of symptomatic and asymptomatic patients older than 65 years with Grade 1 subclinical hyperthyroidism (0.1 < TSH < 0.39 mIU/L) and increased cardiovascular risks may be considered. Young patients (aged < 65 years) with Grade 1 subclinical hyperthyroidism can be observed, whereas Grade 2 subclinical hyperthyroidism treatment depends on the clinical picture. The treatment of subclinical hyperthyroidism is similar to that of overt hyperthyroidism.

Are the treatment options for hyperthyroidism associated with toxic nodules or hyperfunctioning multinodular goiter different from that of Graves' hyperthyroidism?

- Yes. A hyperfunctioning nodule or goiter cannot be healed by antithyroid drugs. Administration of antithyroid drugs can certainly normalize thyroid hormone levels, but after stopping these, hyperthyroidism invariably returns. Only ablative therapies, i.e., radioiodine, and surgery can be used for the definitive treatment of hyperfunctioning nodules. However, antithyroid drugs are needed in the preparation for surgery to make the patient euthyroid before the intervention.

Case Presentation Continued

The young female patient had Graves' disease. TRAb was positive, and ultrasound showed the typical signs for thyroiditis, whereas scintigraphy revealed a diffusely increased Tc uptake in the thyroid bed. Therefore, an antithyroid drug 30 mg methimazole/day and 3 × 20 mg propranolol therapy were launched.

Three weeks after therapy initiation, the patient observed urticariform rashes on her skin. Propranolol was stopped, but nothing had changed. So methimazole was stopped for a few days, and the skin rash then disappeared. Methimazole was changed to propylthiouracil as a second-line antithyroid drug. For her mild eye symptoms, eye drops, pentoxifylline 3 × 400 mg, and 150 mg selenium were given.

Peripheral hormones returned to the reference range after a few months of treatment, and the patient's symptoms significantly improved. TSH remained suppressed. After 18 months of treatment, the patient had a long-term euthyroid state, so antithyroid drug treat-

ment was stopped. Regular checkups continued, and TSH showed an euthyroid state; however, TRAb remained positive, and ultrasound showed discrete thyroiditis signs.

The laboratory results of the patient are presented in Table 12.2.

Two years after the antithyroid drug was stopped, the patient was admitted again to the endocrine unit with the same signs of hyperthyroidism as before. Laboratory results confirmed the recurrence of Graves' disease (2019.04. TSH, < 0.01 mIU/L; fT4, 22 pmol/L; fT3, 8.4 pmol/).

We discussed the possible alternative treatment options with the patient and agreed upon an ablative therapy. Since the thyroid size was not enlarged, and there was no nodule in the thyroid, radioiodine treatment was the choice. 480 MBq doses of ^{131}I radioiodine therapy was given. Three months after the treatment, overt hypothyroidism was developed, and levothyroxine substitution was launched.

Table 12.2 Laboratory results of the patient in the course of disease

Date of blood sampling	TSH (mIU/l) normal: 0.4–4.5	fT4 (pmol/L) normal:12–22	fT3 (pmol/L) normal:3–7	TRAb IU/L normal:<1
09.2015	*0.02 mIU/L*	*28 pmol/L*	*11.1 pmol/L*	*24.9 IU/L*
01.2016	*0.05 mIU/L*	21 pmol/L	*8.7 pmol/L*	
02.2016	*0.08 mIU/L*	18 pmol/L	5.4 pmol/L	
05.2016	*0.05 mIU/L*	20 pmol/L	5.8 pmol/L	
07.2016	*0.00 mIU/L*	*36 pmol/L*	*33 pmol/L*	*1.2 IU/L,*
08.2016	*0.01 mIU/L*	13.7 pmol/L	*7.3 pmol/L*	
10.2016	*<0.01 mIU/L*	8.40 pmol/L	5.80 pmol/L	
04.2017	1.5 mIU/L	10 pmol/L,	6.4 pmol/L	
11.2017	3.5 mIU/L	11.2 pmol/L	5.5 pmol/L	*5.3 IU/L*
07.2018	1.4 mIU/L	12.3 pmol/L	5.8 pmol/L	
10.2018	1.01 mIU/L			

Tips

The reader is advised to read the chapter on thyroid nodule and multinodular goiter (▶ Chap. 15), the next two chapters on thyroid storm and endocrine orbitopathy (▶ Chaps. 13 and 14), and the chapter on thyroid diseases in pregnancy (▶ Chap. 21). Thyroiditis can also be associated with transient forms of hyperthyroidism; therefore, ▶ Chap. 16 on subacute (de Quervain's) thyroiditis can be interesting to the reader. Amiodarone-induced thyroiditis can cause severe hyperthyroidism, as well (▶ Chap. 17).

Take-Home Messages

- Graves' disease is an autoimmune thyroiditis with hyperthyroidism.
- TRAb is the autoimmune marker of the disease.
- Thyroid scintigraphy shows a diffusely increased isotope uptake in the thyroid gland.
- Overt hyperthyroidism is needed to treat, whereas decision for treatment in case of subclinical form should be made individually.

- The choice of treatment is first-line medical therapy with antithyroid drugs and beta-blockers.
- Ablative therapy options are radioiodine or near-total thyroidectomy.
- The most common extrathyroidal manifestation is the endocrine orbitopathy with various severities.
- Pregnant women need special considerations with Graves' disease.

Suggested Reading

1. Bartalena L. Diagnosis and management of Graves disease: a global overview. Nat Rev Endocrinol. 2013;9:724–34. https://doi.org/10.1038/nrendo.2013.193.
2. Bartalena L, Chiovato L, Vitti P. Management of hyperthyroidism due to Graves' disease: frequently asked questions and answers (if any). J Endocrinol Invest. 2016;39(10):1105–14. https://doi.org/10.1007/s40618-016-0505-x.
3. Brent GA. Clinical practice. Graves' disease. N Engl J Med. 2008;358(24):2594–605. https://doi.org/10.1056/NEJMcp0801880.
4. Burch HB, Cooper DS. Management of Graves disease: a review. JAMA. 2015;314(23):2544–54. https://doi.org/10.1001/jama.2015.16535.
5. Kahaly GJ, Bartalena L, Hegedüs L, Leenhardt L, Poppe K, Pearce SH. 2018 European thyroid association guideline for the management of Graves' hyperthyroidism. Eur Thyroid J. 2018;7:167–86. https://doi.org/10.1159/000490384.
6. Kotwal A, Stan M. Current and future treatments for Graves' disease and Graves' ophthalmopathy. Horm Metab Res. 2018;50(12):871–86. https://doi.org/10.1055/a-0739-8134.
7. Laurberg P, Andersen SL. Endocrinology in pregnancy: pregnancy and the incidence, diagnosing and therapy of graves' disease. Eur J Endocrinol. 2016;175(5):R219–30. https://doi.org/10.1530/EJE-16-0410.
8. Piantanida E, Tanda ML, Lai A, Sassi L, Bartalena L. Prevalence and natural history of Graves' orbitopathy in the XXI century. J Endocrinol Invest. 2013;36(6):444–9. https://doi.org/10.3275/8937.
9. Smith TJ, Hegedus L. Graves' disease. N Engl J Med. 2016;375(16):1552–65. https://doi.org/10.1056/NEJMra1510030.
10. Weetman AP. Graves' disease. N Engl J Med. 2000;343(17):1236–48. https://doi.org/10.1056/NEJM200010263431707.

Thyroid Storm

Gabor Laszlo Kovacs

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_13

Opening

In this chapter, the reader will get information about the clinical features, diagnosis and treatment of thyroid storm, which is a severe, life-threatening form of hyperthyroidism. The differential diagnosis of hyperthyroidism and other thyroid disorders are discussed in different chapters.

Definition of the Disease

Thyroid storm is a severe, life-threatening health disorder that is associated with under-treated or untreated hyperthyroidism. Without immediate, aggressive medical intervention, thyroid storm is often fatal. During thyroid storm, the patient's heart rate, blood pressure and body temperature can increase to dangerously high levels that cause atrial fibrillation and other malignant arrhythmias. According to the severity of disease, mild to serious neurological symptoms can develop, but the most probable cause of death is cardiac failure.

Case Presentation

A 38-year-old woman presented to an outpatient clinic with the following symptoms: orthopnoea and increasing peripheral oedema, tachycardia, high frequency atrial fibrillation and biventricular heart failure. Further questioning revealed a 6-month history of weight loss, heat intolerance, diarrhoea, palpitations and nervousness. Two typical symptoms were also recorded: orbitopathy and soft tissue inflammation which included caruncular oedema, chemosis, conjunctival redness, lid redness (Fig. 13.1) and goitre.

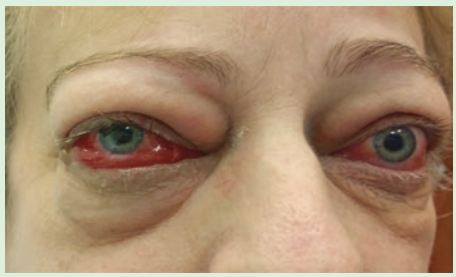

Fig. 13.1 The patient's eyes showing severe endocrine orbitopathy with soft tissue inflammation including caruncular oedema, chemosis, conjunctival redness and lid redness

What kind of disease is the most probable based on these symptoms?

The patient presented typical symptoms of hyperthyroidism; moreover the presence of orbitopathy would suggest Graves' disease.

She had a positive family history for autoimmune thyroid disease. Half a year before the current presentation, hyperthyroidism has been detected by an endocrine outpatient clinic, and anti-thyroid drug was suggested, but the patient did not follow the recommended therapy. The patient now showed signs of a high-frequency atrial fibrillation (132 beats per minute) and tachypnoea (21 breaths per minute). Furthermore, the patient's body temperature was mildly elevated (between 37.0 °C and 37.2 °C). Laboratory testing showed a hormonal panel typical for hyperthyroidism:

- Thyroid-stimulating hormone (TSH) <0.1 mIU/L (normal, 0.42 to 4.32 mIU/L)
- Free thyroxine (fT4) 87.2 pmol/l (normal, 11.5–22.7 pmol/l)
- Free triiodothyronine (fT3) 27.6 pmol/l (normal 2.8–6.5 pmol/l)

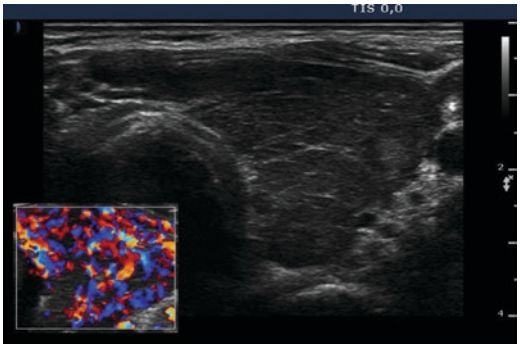

Fig. 13.2 Ultrasound images showing hypervascularity and a hypoechoic pattern of the thyroid gland

Bedside ultrasound revealed hypervascularity and a hypoechoic pattern of the thyroid gland (Fig. 13.2). As expected, the patient also had an elevated thyroid receptor antibody (TRAb) concentration of 18 IU/L (normal, 0–2.0 IU/L), thus confirming the diagnosis of Graves' disease (► Chap. 12).

What are the aetiological factors of thyroid storm?

Thyroid storm, a synonym of thyrotoxic crisis, is an uncommon condition due to an extreme form of thyrotoxicosis. The disease is rare; however, mortality rates may reach 10–20%. The most common cause of thyroid storm is Graves' hyperthyroidism, but it can be associated with several other medical conditions as well.

In most cases, there is an underlying aetiology of hyperthyroidism (like in the cited case – a half year history of un- or undertreated thyrotoxicosis), but the transition to thyroid storm usually requires a second trigger impulse. Usually these are infection, trauma or neck surgery, pregnancy or postpartum period, myocardial infarction and diabetic ketoacidosis. Large amounts of exogenous iodine (such as use of iodinated contrast agents or long-term administration of amiodarone) or prolonged exposure to thermal water with high iodine content (for several days) can provoke thyroiditis or hyperthyroidism. Discontinuation of antithyroid treatment or poor patient adher-

Case Continued

Chest X-ray demonstrated cardiomegaly and pulmonary congestion. An echocardiogram showed a significantly dilated left ventricle with an ejection fraction of 10 to 20 percent. The patient was given 40 mg furosemide two times a day (with potassium substitution) and started on beta-adrenergic blockade by 40 mg propranolol three times a day. As thyrostatic treatment, 10 mg methimazole three times a day was started, and 32 mg methylprednisolone once per day was also given.

Despite the above treatment, the patient's status worsened; the Burch-Wartofsky Point Scale (BWPS) (see below) was above 45, so it was highly suggestive for thyroid storm, and therefore rapid and aggressive multimodal management in an Intensive Care Unit was started. The patient's most critical symptom was cardiac failure. The treatment included high-dosage thiamazole (20 mg three times a day) and 80 mg of parenteral methylprednisolone administered every 8 hours. One day later, Lugol's (iodine) solution was started (ten drops orally in every 8 hours) to decrease the thyroid hormone release. The multidisciplinary medical care team suggested plasmapheresis and immediate total thyroidectomy. Endocrinologists and endocrine surgeons collaborated to perform a total thyroidectomy. Pathological examination revealed small multinodular goitre and follicular hyperplasia consistent with Graves' disease. Following total thyroidectomy, the patient improved, and 3 days after the operation, thyroid hormone replacement therapy was initiated. This resulted in gradual improvement in the ejection fraction (from 10% to 40%), but the patient's cardiac function remained suboptimal for an additional year.

This case is a typical course of the disease, but in more severe cases, for example, in respiratory insufficiency or hypotension intra-aortic balloon pump placement, intubation with artificial ventilation may be necessary.

ence to treatment is associated with worsening of thyrotoxicosis. New biological treatments (such as interleukin-2 and α-interferon, etc.) have been published to generate hyperthyroidism and thyroid storm, too.

What are the symptoms of thyroid storm?

The symptoms of a thyroid storm are not simple exaggerations of the typical manifestation of severe hyperthyroidism. Thyrotoxic crisis, in addition to the presentation of known hyperthyroidism symptoms, can progress into systemic decompensation leading to multiple organ failure and death. The scoring system recommended by Burch and Wartofsky (Table 13.1) describes the typical signs of organ dysfunction and failure, as defined in thyroid storm (thyrotoxic crisis).

Even though the patient in the presented case had only mildly elevated body temperature, fever is a typical finding in thyroid storm. Therefore, the diagnosis of thyroid storm should always be considered in febrile patients with known thyrotoxicosis.

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Fever and persistent sweating generate increased water, sodium, calcium, magnesium and potassium loss leading to complications like dehydration and electrolyte imbalance. Tachyarrhythmias and consecutive cardiac decompensation are common and usually of atrial origin. Ventricular arrhythmias can also occur with the deterioration of the potassium or magnesium and other ion homeostasis. Cardiac failure manifested as peripheral oedema in our patient and even pulmonary congestion is not uncommon when the symptoms are severe. Depending on the fT4 and fT3 levels and the duration of the untreated or undertreated period, the neurological dysfunction may be considerable, manifesting itself in delirium, agitation or psychosis. As a consequence of the presence of cardiac failure or a direct effect of the increased thyroid hormone level itself, liver dysfunction with or without jaundice may also be present. Diarrhoea is a known effect of hyperthyroidism, and it is not different from what is seen in other hyperthyroid situations. Long-term thyrotoxicosis can be associated with a reduced adrenocortical reserve. Moreover, autoimmune hyperthyroidism can rarely be associated with Addison's disease (primary adrenal insufficiency) as parts of the autoimmune polyendocrine syndrome type 2 (▶ Chap. 31).

What are the main diagnostic steps of thyroid storm?

Elevated serum thyroid hormone levels (fT3 and fT4) with suppressed TSH levels confirm the diagnosis of hyperthyroidism. The diagnosis of thyrotoxic crisis is based upon suspicious but nonspecific clinical symptoms, and the previously mentioned *Burch-Wartofsky scores* (Table 13.1). If the diagnosis of thyroid storm is highly suspected based on the clinical presentation and medical history, waiting for the results of laboratory tests to confirm the diagnosis may lead to delayed and thus less efficacious life-saving treatment. Furthermore, highly increased thyroid hormone levels can be observed without severe clinical features; therefore the diagnosis should be set up by clinical signs alone such as physiological parameters (thermoregulatory disorder (fever), cardiac failure and arrhythmia, central nervous system dysfunction, etc.). In most cases, thyroid storm occurs with an underlying predisposition to thyrotoxicosis; therefore it is important to look for possible precipitating factors such as infection, iodine exposure, pregnancy and previous thyroid disease in anamnestic data (Fig. 13.3).

What is the treatment algorithm for thyroid storm?

After the diagnosis of thyroid storm, the patient should be managed immediately in an Acute Medical Unit or Intensive Care Unit. The boundary between severe thyro-

Table 13.1 Diagnostic criteria for thyroid storm: The Burch-Wartofsky Point Scale

Body temperature		Cardiovascular dysfunction		Congestive heart failure		Atrial fibrillation		CNS dysfunction		GI-hepatic dysfunction		Previous episode of thyroid storm	
°C	Point	Tachycardia Beats/min	Point		Point		Point		Point		Point		Point
37.2–37.7	**5**	<99	**0**	Absent	**0**	Absent	**0**	Absent	**0**	Absent	**0**	Absent	**0**
37.8–38.2	**10**	99–109	**5**	Mild (pedal oedema)	**5**	Present	**10**	Mild (agitation)	**10**	Moderate (diarrhoea, nausea/vomiting, abdominal pain)	**10**	Present	**10**
38.3–38.8	**15**	110–119	**10**	Moderate (pulmonary basal rales)	**10**			Moderate (delirium, psychosis, extreme lethargy)	**20**	Severe (jaundice)	**20**		
38.9–39.4	**20**	120–129	**15**	Severe (pulmonary oedema)	**15**			Severe (seizures, coma)	**30**				
39.5–39.9	**25**	130–139	**20**										
≥40	**30**	≥140	**25**										
Total (points from each column are added)													
25–44				**Suggestive of impending storm**									
>45				**Thyroid storm is highly likely**									

Based on Burch and Wartofsky [2], see reference
CNS central nervous system, *GI* gastrointestinal

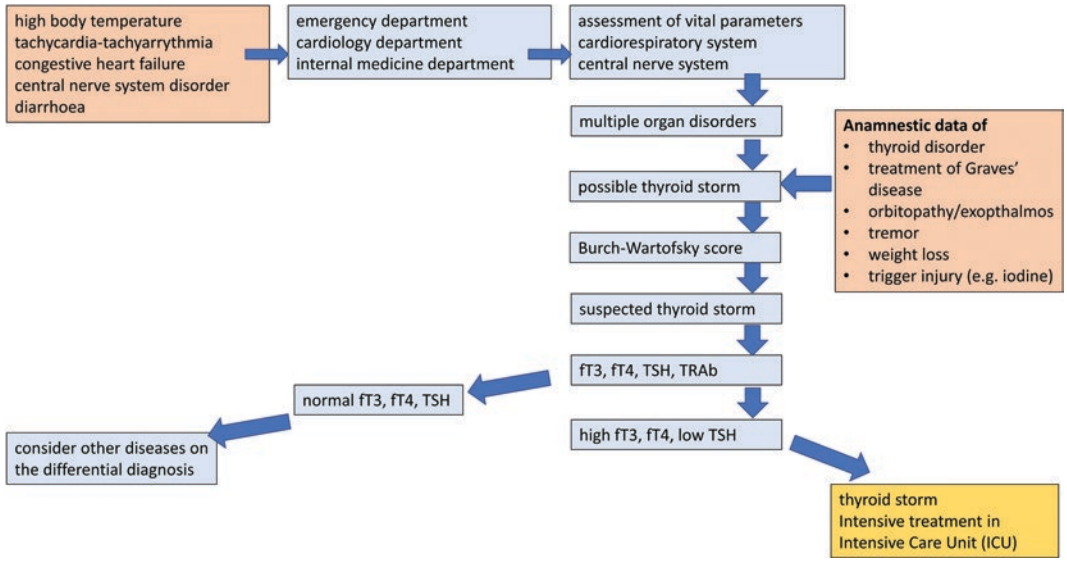


Fig. 13.3 Algorithm for diagnostic steps in thyroid storm

toxicosis and thyroid storm is narrow; therefore close monitoring of vital parameters is crucial.

- Rescue care includes cooling intervention against increased body temperature with antipyretics, but salicylates (e.g. aspirin) should be avoided as they facilitate the displacement of thyroid hormone from thyroid-binding globulin (TBG); therefore acetaminophen (paracetamol) is preferable.

- Maintaining the physiological fluid-electrolyte homeostasis can help in avoiding cardiac arrhythmia. Tachyarrhythmias can be associated with haemodynamic instability and should be managed carefully either with drugs (anti-arrhythmic) or direct coupled (DC) cardioversion.

- Ventilatory support should be provided when necessary, either with non-invasive positive-pressure ventilation (NIPPV) or invasive ventilation. Severe agitation is a frequent symptom in thyroid storm, which endangers the adequate treatment; therefore sedative drugs such as haloperidol, or a benzodiazepine (e.g. clonazepam), should be given carefully, taking into account the possible respiratory depressive side effects of these agents.

- As hyperthyroidism results in negative energy balance, nutritional support focusing on thiamine and other vitamin supplements is also recommended. Continuous blood glucose monitoring is suggested because liver glycogen stores are used up by thyroid hormones. Beyond the above-mentioned adjuvant treatment and supports, targeted therapy is needed with a focus on decreasing thyroid hormone synthesis and release and peripheral action of circulating thyroid hormone.

- The suggested therapeutic approach is the same as in severe thyrotoxicosis, but with a strong focus on higher dosage and frequency of medical treatment and on a more holistic adjuvant treatment (Table 13.2). We can block the thyroid hormone effect at five levels:
  1. *Block* thyroid hormone synthesis (by anti-thyroid drugs).
  2. *Block* hormone release (by iodine).
  3. *Block* the active peripheral hormone synthesis, the T4 into T3 conversion (by propranolol, propylthiouracil [PTU], corticosteroids).

Table 13.2 Drug treatment options in thyroid storm

Medication	Dose	Mechanism and effects
Propylthiouracil (PTU)	600 mg loading dose, followed by 200–250 mg PO every 4–6 hours	Inhibition of hormone synthesis Peripheral de-iodination
Methimazole/carbimazole	20–30 mg PO every 4–6 hours	Inhibition of hormone synthesis
With regard to severe liver toxicity with high-dose PTU, methimazole (or carbimazole) is the preferable thionamide. Consecutive liver function and blood count control suggested		
Lugol's solution	5–10 drops PO every 6–8 h	Inhibition of hormone release
Administer at least 1–6 hours (or even 1 day) after initiation of thionamide		
Propranolol	1–2 mg/min IV every 15 min up to max 10 mg or 40–80 mg PO every 4–6 h	Inhibition of peripheral conversion of T4 into T3
Metoprolol	1–2 mg/min IV every 15 min up to max 10 mg or 50–100 mg PO every 6 h	Inhibition of peripheral conversion of T4 into T3
Hydrocortisone	100 mg IV every 6 h	Inhibition of peripheral conversion of T4 into T3
Dexamethasone	2 mg IV every 6 h	Inhibition of peripheral conversion of T4 into T3
Improve the secondary adrenal insufficiency and autoimmune thyroiditis if exists		
Acetaminophen (paracetamol)	500–1000 mg PO every 6 h	Decrease body temperature
It can worsen hepatic dysfunction		
Lithium carbonate	300 mg PO every 8 hours	Inhibits thyroid hormone release from the gland
Potassium perchlorate	1 g PO od	Inhibits iodide transport into the thyrocyte
Cholestyramine	4 g PO every 6–12 hours	Reduces the reabsorption of thyroid hormone from the enterohepatic circulation

Based on Carroll and Matfin [3], see reference
PO oral, IV intravenous, od once daily

4. *Block* the most important cardiac symptoms (tachycardia/tachyarrhythmia) by beta-blocker drugs.
5. In some sources, treatment for *blocking* the enterohepatic circulation (i.e. cholestyramine) is also proposed.

Thionamide drugs should be administered without any delay. Thionamides inhibit the coupling of iodothyronines and therefore reduce the synthesis of the thyroid hormone. All inhibit the function of the thyroid peroxidase enzyme, reducing organification and oxidation of iodide. Either PTU or carbimazole (or methimazole) can be used. Carbimazole is not an active drug; it has to be decarboxylated to methimazole in the liver. PTU has a more rapid onset of action and inhibits peripheral deiodinase enzyme (results in a lower conversion of T4 into T3), but it has a higher liver toxicity potential than other thionamides. Thionamides can be administered orally or via a nasogastric (NG)

tube (or even rectally) in unconscious patients with a loading dose of 600 mg followed by a dose of 200–250 mg every 4–6 hours for PTU or 20–30 mg every 4–6 hours for carbimazole (or methimazole). Consecutive control of liver function and full blood count (focusing on neutropenia) is highly recommended as abnormalities of the liver are the most frequent side effect of high-dose thionamides.

Beta receptor-blockers (BB) should be administered without any delay (unless contraindicated, e.g. severe bronchial asthma, chronic obstructive pulmonary disease). Propranolol, as a non-cardiac specific BB, is a first-line therapy, because it has proven effect on inhibition of T4 into T3 conversion. In some countries, propranolol is accessible for intravenous (IV) use also. IV propranolol at a dose of 1–2 mg/min can be administered every 15 minutes up to the maximum dose of 10 mg, followed by 40–80 mg orally every 4–6 hours. In the absence of IV propranolol, metoprolol can be used as an effective BB (a dose of 1–2 mg/min can be administered every 15 minutes up to the maximum dose of 10 mg under continuous ECG monitoring). Alternatively, calcium channel blockers such as short-acting verapamil can be used at a dose of 40 mg orally every 6–8 hours or 5–10 mg (0.075–0.15 mg/kg) by IV, but BBs are highly preferable. If anticoagulation is required for atrial fibrillation, patients experiencing thyroid storm react very sensitively to warfarin administration; therefore in these situations, low-molecular-weight heparins (e.g. nadroparin, enoxaparin) are recommended.

Iodine is an effective suppressor of thyroid hormone release (Wolff-Chaikoff effect), but it should be administered at least 1–6 hours after thionamide to prevent unwanted tyrosine residue iodination and accumulation of thyroid hormone stores. In our practice, we use it 1–2 days after the initial treatment. The effect lasts for up to 2 weeks, therefore unsuitable as a long-term therapy. Iodine administration might worsen the symptoms after 2 weeks; therefore definitive treatment (total thyroidectomy) must be done after iodine therapy. The iodine treatment usually means Lugol's solution in the endocrine practice, given 5–10 drops orally every 6–8 hours.

Corticosteroids inhibit peripheral conversion of T4 into T3, and as adrenal insufficiency might also occur in thyrotoxic crisis, administration of these drugs may improve the outcomes. Dexamethasone 2 mg IV every 6 hours can be used, or hydrocortisone 100 mg 6 hourly should be given IV or IM. The doses should be tapered gradually as the symptoms of thyroid storm improve.

Adjuvant Medical Treatments

Potassium perchlorate competitively inhibits iodide transport into the thyrocyte, but mainly it is particularly useful in amiodarone-induced thyrotoxicosis. A suggested dose is 1 g daily and is advised to be combined with a thionamide.

Lithium carbonate can be an alternative treatment at a dose of 300–500 mg every 8 hours, if there is a contraindication to thionamide therapy (e.g. neutropenia during former administration of a thionamide or allergy), but continuous serum lithium levels should be monitored to avoid exceeding the normal range. Lithium inhibits thyroid hormone release and reduces iodination of tyrosine residues.

Cholestyramine 4 g orally two to four times per day reduces the reabsorption of metabolized thyroid hormone from the enterohepatic circulation; therefore it diminishes the active hormone level.

What is the definitive treatment of thyroid storm?

Our experience is that the definitive *total thyroidectomy* cannot be avoided in thyroid storm, because in most cases, the disease is refractory to any of the abovementioned treatment options, or the patient's medical condition worsens. As

the thyrotoxic crisis can facilitate the appearance of malignant arrhythmias during anaesthesia, plasmapheresis for removal of the thyroid hormone is highly recommended to prepare the patient for surgery. As mentioned in our case, plasmapheresis needs to be repeated at least 2–3 times as only a small fraction of thyroid hormones can be removed during a session. The minimal aim of plasmapheresis to reach the upper limit of normal range of T4 and the surgery should be organized *immediately* after the last plasmapheresis session.

Tips

The reader is advised to read the preceding chapter on Graves' disease (▶ Chap. 12) and the chapter on Addison's disease (▶ Chap. 31).

Take-Home Messages

- Thyroid storm is a rare but severe endocrine disorder, and immediate diagnosis of this dangerous status can be lifesaving.
- A multimodal treatment approach to patients with thyroid storm is recommended, including anti-thyroid drug therapy, glucocorticoid administration, beta-adrenergic blockade, cooling blankets, volume resuscitation, nutritional support, respiratory care and monitoring in an Intensive Care Unit.
- The anti-thyroid drug therapy targets to block thyroid hormones at all possible levels: the thyroid hormone synthesis, the release of thyroid hormone from thyroid stores and the peripheral effects of thyroid hormone excess.
- The medical therapy can stabilize the status, but a definitive resolution—such as surgery—should be pursued.

Suggested Reading

1. Akamizu T, Satoh T, Isozaki O, Suzuki A, Wakino S, Iburi T, Tsuboi K, Monden T, Kouki T, Otani H, Teramukai S, Uehara R, Nakamura Y, Nagai M, Mori M, Japan Thyroid Association. Diagnostic criteria, clinical features, and incidence of thyroid storm based on nationwide surveys. Thyroid. 2012;22(7):661–79. https://doi.org/10.1089/thy.2011.0334.
2. Burch HB, Wartofsky L. Life-threatening thyrotoxicosis: thyroid storm. Endocrinol Metab Clin N Am. 1993;22:263–77.
3. Carroll R, Matfin G. Endocrine and metabolic emergencies: thyroid storm. Ther Adv Endocrinol Metab. 2010;1(3):139–45. https://doi.org/10.1177/2042018810382481.
4. Ezer A, Caliskan K, Parlakgumus A, Belli S, Kozanoglu I, Yildirim S. Preoperative therapeutic plasma exchange in patients with thyrotoxicosis. J Clin Apharesis. 2009;11:111–4. https://doi.org/10.1002/jca.20200.
5. Kahaly GJ, Bartalena L, Hegedüs L, Leenhardt L, Poppee K, Pearce SH. 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. Eur Thyroid J. 2018;7:167–86. https://doi.org/10.1159/000490384.
6. Satoh T, Isozaki O, Suzuki A, Wakino S, Iburi T, Tsuboi K, Kanamoto N, Otani H, Furukawa Y, Teramukai S, Akamizu T. 2016 Guidelines for the management of thyroid storm from The Japan Thyroid Association and Japan Endocrine Society (first edition). Endocr J. 2016;63(12):1025–64. https://doi.org/10.1507/endocrj.EJ16-0336.

Endocrine Orbitopathy

Endre V. Nagy

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_14

Opening

In this chapter, the reader will get acquainted with the clinical features, diagnosis and management of endocrine orbitopathy (EO). EO is an autoimmune disease of the orbits, which accompanies Graves' disease in up to 30% of the cases.

Definition of the Disease

Endocrine orbitopathy (synonyms: Graves' ophthalmopathy, endocrine ophthalmopathy, thyroid eye disease) is an autoimmune inflammation of the orbital tissues. EO usually manifests contemporaneously with Graves' hyperthyroidism; however, in the minority of cases, EO may precede or follow it by several months. Rarely, EO may be associated with Hashimoto thyroiditis. The major characteristics of the orbital process are immune cell infiltration, local cytokine production, fibroblast proliferation and connective tissue matrix expansion. These, combined with swelling and dysfunction of the external eye muscles, cause proptosis, diplopia, lagophthalmos (incomplete closure of the eyelids) and consequent exposure and inflammation of the conjunctival and corneal surface. The most severe cases present with chemosis (extensive swelling and oedema of the conjunctiva). Rarely, compression of the optic nerve by enlarged rectus muscles may result in rapid deterioration of visual acuity ending in permanent sight loss. Exposure and dryness of the corneal surface may lead to corneal ulceration.

Case Presentation

A 35-year-old woman was referred to our endocrine clinic for bilateral proptosis, upper lid swelling, diplopia and redness of the eyes (Fig. 14.1). She was diagnosed with Graves' hyperthyroidism 3 months earlier by her primary care physician, with elevated FT4 and FT3 and suppressed TSH levels. By palpation and ultrasound, a mildly enlarged, non-nodular thyroid gland was detected. The diagnosis was supported by the high level of TSH receptor antibody (TRAb) in her sera. By the primary care physician, eye signs of Graves' hyperthyroidism were seen, but no complaints or signs suggestive of EO were present. Her thyroid hormone levels gradually decreased on medical treatment (thiamazole 30 mg/day) and were only mildly elevated on presentation at our endocrine clinic.

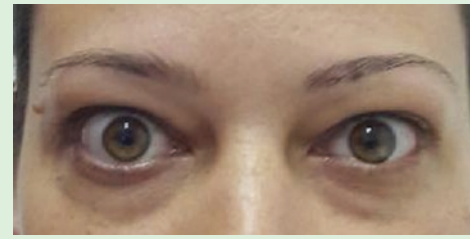


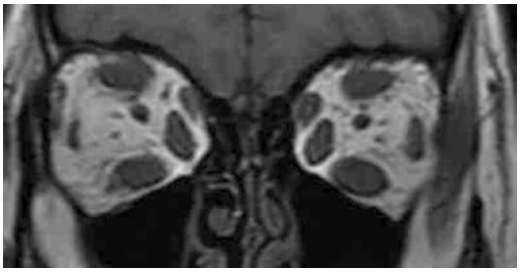
Fig. 14.1 Endocrine orbitopathy. Exophthalmos (right, 23 mm; left 21 mm; upper normal 18 mm), upper eyelid oedema and lid retraction. Double vision was present in right and left lateral gaze. In the referral letter, conjunctival redness was also reported, which disappeared after artificial tears were prescribed

How can we confirm the diagnosis of EO? What other diseases may resemble EO?

In patients with current or recent Graves' hyperthyroidism, the presence of the characteristic eye signs confirms the diagnosis of EO (▶ Box 14.1). Ophthalmology consultation at this stage and later during follow-up is essential. In less than 5% of the cases, when EO is the presenting disease and no thyroid dysfunction can be found, the diagnosis may be challenging. The majority of these patients have detectable TRAb in their sera. More than two thirds of EO cases are clinically symmetric, and in more than 90% of seemingly one-sided disease, some characteristics of EO are present in the contralateral side by MR (◘ Fig. 14.2). Imaging may be required to rule out other possible causes of proptosis. Orbital tumour is detectable by CT or MR, as are other rare diseases of the region. IgG4-related disease of the orbits may resemble EO by imaging; it can be confirmed by the several-fold increase in serum IgG4 level.

Box 14.1 Signs of Endocrine Orbitopathy

- Lid aperture ('widely open eyes') – measured in primary gaze with distant fixation (mm)
- Soft tissue inflammation – swelling or redness in the anterior segment (eyelid, conjunctiva)
- Exophthalmos – by Hertel's exophthalmometry; increasing or side difference (mm)
- Diplopia – intermittent or permanent; all directions or in certain directions of gaze
- Impaired vision
  - corneal involvement – keratopathy, corneal ulcer
  - optic neuropathy – decreased VEP (visual evoked potential), decreased CFF (critical fusion frequency), visual filed defect, decreasing visual acuity



◘ **Fig. 14.2** MR coronal T1 image. In both orbits, the inferior and medial rectus muscles are enlarged, which is a frequent finding in EO

How can we, and why is it important to, detect EO at an early stage of the orbital autoimmune process?

Signs of EO need to be looked for at each follow-up visit of patients with Graves' disease. Eye discomfort, conjunctival redness and pain behind one or both eyes are early signs. The earlier we diagnose the orbital process, the better the chances are to slow or stop progression by specific treatment.

What is the difference between the eye signs of Graves' hyperthyroidism and signs of EO?

The classical eye signs of Graves' disease (Graefe's, Stellwag's, Möbius' and Dalrymple's) are fully reversible with the restoration of euthyroidism. EO signs and symptoms (▶ Box 14.1) are not, as EO follows a completely different disease course, which may continue for months or years after successful treatment of hyperthyroidism.

Is EO always symmetric?

Usually, as in the present case, signs and symptoms are of comparable severity on both sides. Sometimes, a marked asymmetry is detectable; however, the immune process is present in both orbits, and treatment measures, e.g. irradiation, should target both orbits. Variations in orbital anatomy may account for side differences in some patients.

Does clinical severity (as deemed by the criteria shown in ▶ Box 14.2) reflect the activity of the orbital autoimmune process?

Unfortunately, it does not. The start and peak of the autoimmune process precede the clinical manifestation of EO. Together with clinical severity, disease activity also has to be estimated, because immune suppressive treatments are ineffective in the absence of immune activity, while their side effects remain the same. The easiest approach for activity estimation is the clinical activity score (CAS; ◘ Table 14.1). In case of doubt, oedema (water content) of the eye muscles may be measured by MR or orbital inflammation detected by nuclear techniques (labelled somatostatin analogues or diethylenetriaminepentaacetic acid SPECT).

Box 14.2 Disease Severity in Endocrine Orbitopathy

No EO

Normal eyes

Eye signs of Graves' hyperthyroidism, with or without redness of the conjunctiva

Mild EO

One or more of the following:

Minor lid retraction (<2 mm)

Mild soft tissue involvement

Exophthalmos <3 mm (above normal for race and gender)

No or intermittent diplopia

Corneal signs responsive to lubricants

Moderate to severe EO

Two or more of the following:

Lid retraction ≥2 mm

Moderate or severe soft-tissue involvement

Exophthalmos ≥3 mm (above normal for race and gender)

Permanent diplopia (any severity)

Sight-threatening EO

Corneal ulcer

Optic neuropathy

◘ **Table 14.1** Assessment of the activity of the disease in endocrine orbitopathy: the Clinical Activity Score (CAS) according to the European Thyroid Association and the European Group on Graves' Orbitopathy

Spontaneous retrobulbar pain	Yes/No
Pain on attempted upward or downward gaze	Yes/No
Redness of eyelids	Yes/No
Redness of conjunctiva	Yes/No
Swelling of caruncle or plica	Yes/No
Swelling of eyelids	Yes/No
Swelling of conjunctiva (chemosis)	Yes/No

The number of signs from the above list present is the CAS of the given (right or left) orbit. EO is considered active if CAS ≥3 in one or both eyes (orbits). Although removed from this list during the last update, new-onset diplopia with recent-onset Graves' disease as well as increase of proptosis ≥2 mm in 3 months may also be considered signs of disease activity

What are the predisposing factors to EO, and can we modify them?

The most important predisposing factor is smoking. Immediate and complete abandonment of smoking has comparable beneficial effect to intravenous glucocorticoids (see below). Over- or undertreated hyperthyroidism worsens the orbital process; subclinical hyperthyroidism is considered to be the less harmful thyroid functional state for active EO by many.

The patient we are discussing is on thiamazole. How would alternative treatment choices of hyperthyroidism interfere with her orbital disease?

Medical treatment with thiamazole or other anti-thyroid medication (▶ Chap. 12) is a good choice. As any degree of hypothyroidism may severely impact EO, addition of levothyroxine to thiamazole, as a block-and-replace regime, may help to avoid hypothyroidism while sustaining a full thy-

roid blocking effect. In the present case, when both FT4 and FT3 tend to arrive in the reference range, thiamazole may be supplemented with 50 to 75 ug levothyroxine, instead of reducing thiamazole dose.

In active EO, *radioiodine* is not an option for the treatment of hyperthyroidism. Radioiodine has unfavourable effect on the orbital process. In inactive EO, radioiodine may be used with co-administration of a preventive course of oral corticosteroid; this way, activation or worsening of EO may be avoided. The typical 4 weeks' regime used at our institution starts on day 3 after ^{131}I therapy: methylprednisolone 32 mg for 4 days, followed by 32 mg on alternate days for 8 days, 16 mg on alternate days for 8 days, and then 8 mg on alternate days for 8 days. Early introduction of levothyroxine replacement is a must, as hypothyroidism, even subclinical, rapidly worsens EO.

Total or near thyroidectomy would be an appropriate choice from the point of EO, resulting in excellent orbital outcome 1 year after surgery. This improvement is not present with less than total thyroid surgeries.

In addition to quitting smoking, what other specific treatments are required for our patient?

The treatment is based on disease severity and disease activity. EO in the early stage at presentation is usually active; her CAS was 4/7 on both sides, i.e. the disease was active (■ Table 14.1). Severity was *moderate to severe* on the scale (► Box 14.2): permanent diplopia was present in lateral gaze; Hertel exophthalmometry was: right 23 mm, left 21 mm measured at 102 mm (the normal value in this population is below 18 mm both sides). As a first approach, selenium 200 µg per day and pentoxifylline 2x400 mg per day could be tried combined with the abandonment of smoking. However, due to clear disease activity and a substantial drop in her quality of life, corticosteroid was administered: methylprednisolone venous infusion once a week 500 mg for 6 weeks and 250 mg weekly for another 6 weeks. Alternative choices would have been oral corticosteroid on alternate days (less effective, more side effects) or 20 Gy orbital irradiation (usually second line choice with or without steroids). In addition to the categories listed in ► Box 14.2, quality of life is a major factor in classifying severity: in the mild EO group, the effect of the disease on daily life is insufficient to justify immunosuppressive or surgical treatment, while complaints having a sufficient impact on daily life justify the risks of immunosuppression (in active disease) or surgical intervention (in inactive EO).

What are the options if corticosteroids fail?

A second run of corticosteroids, usually combined with irradiation (see above), may be tried. However, 8000 mg of methylprednisolone in any 12 months' period should not be exceeded due to the risk of acute liver failure. *Anti-CD20 monoclonal antibody* can be used in severe, relapsing cases. The *IGF-1 receptor antibody* teprotumumab may be chosen for the most severe cases; it is the most effective modality in reducing proptosis. The latter two treatments are best performed in specialized thyroid eye clinics.

Progressive loss of visual acuity is a sign of optic neuropathy, usually caused by direct optic nerve compression in the orbital apex by the muscles. If medical treatment fails to achieve the improvement of visual acuity, *orbital decompression surgery* is required with no delay. Depending on the experience of the surgeon, lateral or medial bony wall removal is equally effective; in addition to saving the sight of the patient, all clinical signs and symptoms improve immediately after surgery. Corneal ulcer, another sight-threatening condition, is treated with combined systemic and local measures and may require decompression surgery.

Can we use local treatments?

The exposed corneal and conjunctival surface is large due to the widely open eyes, and tear production may be reduced due to lacrimal gland autoimmunity. Protection of the cornea and conjunctiva can be achieved by frequent application of artificial tears during daytime and protective ointments at night. In patients who are unable to close their eyelids while asleep due to proptosis or lid retraction, special ophthalmological measures may be required. Glasses against sun or wind exposure also help to reduce tear evaporation.

What are the treatment options in the late, inactive phase of the disease?

In moderate to severe EO, proptosis improves with the above treatments in the active phase of the disease, but orbital anatomy nearly never returns to normal. Lid retraction and diplopia may persist due to scar formation at the previous inflammation sites. Eye lid surgery, diplopia correction surgery or, if severe exophthalmos persists, elective bony orbital decompression can be performed in the late stage, usually years after disease onset. The prerequisite of any elective orbital surgical intervention is that CAS does not show disease activity. Two identical objective diplopia tests results, with at least 6 months between them, e.g. two identical Hess charts, may guarantee that the early good result of diplopia surgery will not disappear with further scar formation.

Our patient is young and based on her ID photos used to have a beautiful facial appearance. She has worked at a front desk until recently. Now she has received a desk in the back office. Will the signs of EO disappear with treatment?

Except for mild cases, complete cure of the eye signs is rare. Residual signs may be corrected by surgery (see above). After medical treatment of hyperthyroidism, relapse of Graves' disease may be accompanied by flare-up of EO.

Tips

The reader is advised to read the chapter on Graves' disease (▶ Chap. 12) before reading this chapter.

Take-Home Messages

- In Graves' hyperthyroidism, it is crucial to look for signs of endocrine orbitopathy, as the success of its treatment is dependent on timely introduction of therapy.
- If euthyroid endocrine orbitopathy is suspected, TRAb measurement and orbital imaging may facilitate the diagnosis.
- During the treatment of hyperthyroidism, any level of hypothyroidism may worsen the signs of endocrine orbitopathy.
- Radioiodine therapy should be avoided in patients with active endocrine orbitopathy.
- In moderate to severe cases, the standard effective treatment is a 12 weeks' course of methylprednisolone in weekly infusions.
- Progressive loss of visual acuity prompts immediate intervention; if high-dose steroids are ineffective, orbital decompression surgery is required.

Suggested Reading

1. Bartalena L, Baldeschi L, Boboridis K, Eckstein A, Kahaly GJ, Marcocci C, Perros P, Salvi M, Wiersinga WM, European Group on Graves' Orbitopathy (EUGOGO). The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. Eur Thyroid J. 2016;5(1):9–26. https://doi.org/10.1159/000443828.
2. Bartalena L, Marcocci C, Bogazzi F, Panicucci M, Lepri A, Pinchera A. Use of corticosteroids to prevent progression of Graves' ophthalmopathy after radioiodine therapy for hyperthyroidism. N Engl J Med. 1989;321(20):1349–52. https://doi.org/10.1056/NEJM198911163212001.
3. Campi I, Vannucchi G, Salvi M. Endocrine dilemma: management of Graves' orbitopathy. Eur

J Endocrinol. 2016;175(3):R117–33. https://doi.org/10.1530/EJE-15-1164.
4. Coulter I, Frewin S, Krassas GE, Perros P. Psychological implications of Graves' orbitopathy. Eur J Endocrinol. 2007;157(2):127–31. https://doi.org/10.1530/EJE-07-0205.
5. Dickinson AJ, Perros P. Controversies in the clinical evaluation of active thyroid-associated orbitopathy: use of a detailed protocol with comparative photographs for objective assessment. Clin Endocrinol (Oxf). 2001;55(3):283–303. https://doi.org/10.1046/j.1365-2265.2001.01349.x.
6. Johnson KT, Wittig A, Loesch C, Esser J, Sauerwein W, Eckstein AK. A retrospective study on the efficacy of total absorbed orbital doses of 12, 16 and 20 Gy combined with systemic steroid treatment in patients with Graves' orbitopathy. Graefes Arch Clin Exp Ophthalmol. 2010;248(1):103–9. https://doi.org/10.1007/s00417-009-1214-3.
7. Kahaly GJ, Pitz S, Hommel G, Dittmar M. Randomized, single blind trial of intravenous versus oral steroid monotherapy in Graves' orbitopathy. J Clin Endocrinol Metab. 2005;90(9):5234–40. https://doi.org/10.1210/jc.2005-0148.
8. Mourits MP, Koornneef L, Wiersinga WM, Prummel MF, Berghout A, van der Gaag R. Clinical criteria for the assessment of disease activity in Graves' ophthalmopathy: a novel approach. Br J Ophthalmol. 1989;73(8):639–44. https://doi.org/10.1136/bjo.73.8.639.
9. Stein JD, Childers D, Gupta S, Talwar N, Nan B, Lee BJ, Smith TJ, Douglas R. Risk factors for developing thyroid-associated ophthalmopathy among individuals with Graves disease. JAMA Ophthalmol. 2015;133(3):290–6. https://doi.org/10.1001/jamaophthalmol.2014.5103.
10. Szucs-Farkas Z, Toth J, Balazs E, Galuska L, Burman KD, Karanyi Z, Leovey A, Nagy EV. Using morphologic parameters of extraocular muscles for diagnosis and follow-up of Graves' ophthalmopathy: diameters, areas, or volumes? AJR Am J Roentgenol. 2002;179(4):1005–10. https://doi.org/10.2214/ajr.179.4.1791005.
11. Szucs-Farkas Z, Toth J, Kollar J, Galuska L, Burman KD, Boda J, Leovey A, Varga J, Ujhelyi B, Szabo J, Berta A, Nagy EV. Volume changes in intra- and extraorbital compartments in patients with Graves' ophthalmopathy: effect of smoking. Thyroid. 2005;15(2):146–51. https://doi.org/10.1089/thy.2005.15.146.
12. Terwee C, Wakelkamp I, Tan S, Dekker F, Prummel MF, Wiersinga W. Long-term effects of Graves' ophthalmopathy on health-related quality of life. Eur J Endocrinol. 2002;146(6):751–7. https://doi.org/10.1530/eje.0.1460751.
13. Wang Y, Smith TJ. Current concepts in the molecular pathogenesis of thyroid-associated ophthalmopathy. Investig Ophthalmol Vis Sci. 2014;55(3):1735–48. https://doi.org/10.1167/iovs.14-14002.
14. Werner SC. Modification of the classification of the eye changes of Graves' disease. Am J Ophthalmol. 1977;83(5):725–7. https://doi.org/10.1016/0002-9394(77)90140-4.

Thyroid Nodule and Multinodular Goiter

Tamas Solymosi

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_15

Opening

This chapter discusses the diagnosis of thyroid nodule and multinodular goiter and the treatment of benign forms. Thyroid nodules are one of the most common endocrine disorders; they are mostly benign; however, the diagnosis of malignancy is a crucial issue.

Definition of the Disease

Thyroid nodule (TN) is one of the most common endocrine abnormalities: Palpable nodules are found in 4–7% of the normal population, while discrete lesions can be found in almost every adult. Less than 1% of the thyroid lesions can be life-threatening due to their malignant potential. The evaluation of TNs became quite simple as TSH determination, thyroid ultrasound (US), and fine needle aspiration cytology (FNA) are enough for a complete diagnosis in most cases. One of the main issues is that the US and the FNA are both highly dependent on the examiner, and in contrast to cardiology, US is usually performed not by a specialist of the field but by a radiologist. TNs cannot be treated with drugs; therefore, the basic question regarding a patient with thyroid nodule is whether to operate or not. Recently, nonsurgical methods are getting increasingly available.

Case Presentations

Case Study 1

Clinical presentation A 48-year-old woman was referred for an evaluation of a thyroid nodule which was discovered on an US screening. The patient was told that she had a very suspicious nodule which was described as a TIRADS 5 lesion (see later). The patient was frightened by the information, and since she had got an appointment for a thyroid examination only 3 weeks later, she sought help from her doctor's acquaintances. Thyroid scintigraphy, cervical MRI, and even FDG-PET-CT scan were performed within these 3 weeks at her own expense. Only reactive-type lymph nodes and nonspecific PET positivity were found in the right thyroid lobe.

Palpation exhibited no abnormality.

Hormonal evaluation showed normal thyroid functioning (TSH 1.76 mIU/L).

Ultrasonography The thyroid was echonormal and there were numerous cystic areas in both lobes. They were less than 1 cm in maximal diameter and contained intranodular hyperechogenic granules. The latter were bright and, except for two, presented with the characteristic dorsal narrowing tail of comet-tail artifact (see Fig. 15.1). FNA was performed from two of the lesions, and the cytology resulted in benign cystic-colloid lesions in both locations.

We told her that the possibility of a carcinoma can be excluded and even these lesions cannot be treated as abnormal. However, she visited another thyroidologist too, who did not perform US himself. He told the patient that the risk of carcinoma is minimal but if she cannot bear the existing uncertainty about the diagnosis, it would be better to undergo surgery. A right lobectomy was performed as a result. An intact thyroid with several cystically dilated macrofollicles was described on histopathology.

Case Study 2

Clinical presentation A 71-year-old woman was referred for an aspiration cytology of a "large" nodule before a planned thyroid surgery.

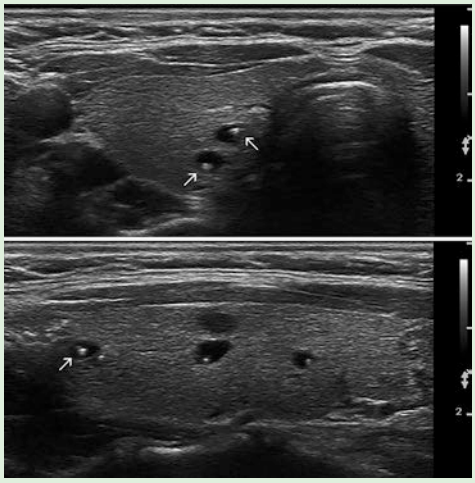


Fig. 15.1 A normal thyroid. The thyroid is echonormal and is not enlarged. There are several cystic areas within the lobe; these are <1 cm in maximal diameter and present comet-tail artifacts – colloid crystals (arrows). The presence of this figure is a very specific sign of a benign lesion, however, is not rarely misinterpreted as microcalcification

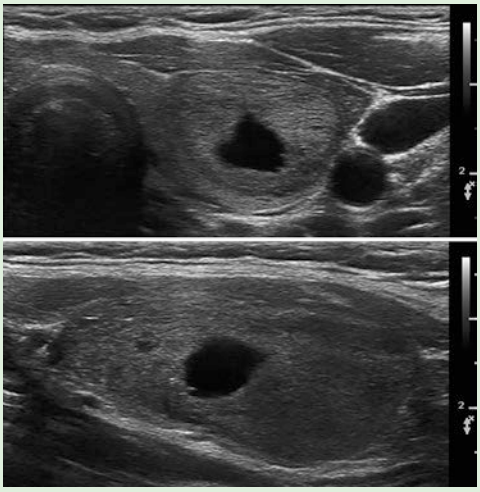


Fig. 15.2 A typical benign thyroid nodule. The nodule is isoechoic (echonormal) and presents halo sign and central-type cystic degeneration. The size of the whole lobe and not the nodule is the decisive factor as to whether a goiter can cause compression in the neck structures. Although the lesion was relatively large, the volume of the lobe was only 8.7 mL which does not mean enlargement

The patient had been aware of her goiter for more than 35 years. She did not notice increase in size or have any other complaints.

Hormonal evaluation indicated euthyroidism (TSH 1.98 mIU/L).

Ultrasound showed an echonormal nodule which presented cystic degeneration and a halo sign. The dimensions of the nodule were 19 × 14 × 40 mm (5.6 mL) while the halo was 23x16x45 mm (8.7 mL) (see Fig. 15.2).

Aspiration cytology revealed a benign cystic-colloid goiter.

We decided to continue monitoring of the lesion in agreement with the patient.

Case study 3

Clinical presentation A 71-year-old woman was referred for a repeated aspiration cytology of a nodule detected by screening. The first cytology performed in another institute resulted in Bethesda III, AUS category (see later).

Palpation exhibited no abnormality.

Laboratory test appeared to be TSH 0.86 mIU/L.

Ultrasonography The thyroid was partly echonormal and partly minimally hypoechoic. There were several more hypoechogenic lesions in both lobes. The largest one in the right lobe had irregular margins and presented clusters of microcalcifications, taller-than-wide shape (see Fig. 15.3).

Cytology showed suspicion of papillary carcinoma.

Right lobectomy was performed and the intranodular frozen section showed a benign lesion. On final histopathology, benign hyperplastic nodules were described.

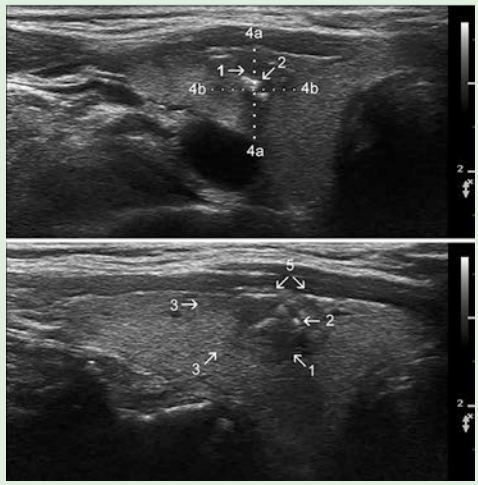


Fig. 15.3 Suspicious ultrasound characteristics in thyroid nodules. The nodule presents all possible suspicious ultrasound characteristics: being deeply hypoechoic (1), having microcalcifications (2), having lobulated borders (3), and displaying taller-than-wide shape (4), i.e., the depth of the nodule (4a) exceeds the width of the lesion (4b). The capsule is discontinuous (5) which is one feature of a possible extrathyroidal spread

How to define a thyroid nodule?

As many methods of examination exist, the nodular goiter is defined in so many different ways. Traditionally, palpation was the basis of the diagnosis. Recently, a TN is determined by US. The issue is that every thyroid disorder, not only TN, appears in the form of discrete lesions, e.g., the most common US sign of autoimmune thyroiditis is the presence of discrete lesions which involve more than 90% of Hashimoto thyroiditis patients.

If the nodule was defined as a discrete US lesion, most adult humans would be labeled as nodular goiter patients. In order to avoid psychological harm and unnecessary cost, we need to separate lesions that are histologically nodules from those that are not, or we have to determine which lesion needs further investigation and which one does not.

Although there is no consensus among experts on how to do this, most protocols determine a maximum diameter of discrete lesions. We do not use the term nodule or do not perform further diagnostic tests below that size. The size limit is 10 mm for those lesions which do not present suspicious signs and 5 mm for those which do.

What are the typical clinical signs of an enlarged thyroid?

A persistent problem with swallowing when consuming solid food is the most reliable and common sign for an enlarged thyroid gland. The cartilaginous-walled trachea is harder to compress with the goiter than the muscular-walled esophagus. Therefore, it is less likely that an enlarged thyroid would cause dyspnea without a swallowing problem. Tracheal X-ray examination is of great help in uncertain cases. Deeper voice is experienced in a thyroid gland of a significant size, as well. Palsy of the recurrent nerve confirmed by a laryngeal examination in any case raises the suspicion of thyroid cancer. In contrast to the former symptoms, the most frequent neck complaint, the "lump in the throat feeling," is usually not caused by a thyroid disease. This is caused by an increase blood supply in the thyroid due to physical or mental issues, which is experienced by a 10–15% of the population.

What are the goals of the evaluation in thyroid nodules?

There are basically two purposes of the examination of a patient. On one hand, it is to decide who is in need of surgery (or other definitive therapy), and, on the other hand, it is to determine what needs to be done for patients who do not require surgery.

How to evaluate a patient with a suspected nodular goiter?

Figure 15.4 summarizes the algorithm of an evaluation. In more than 95% of the newly diagnosed patients, TN, all TSH, US, and FNA are enough to get the diagnosis and to determine further steps. We

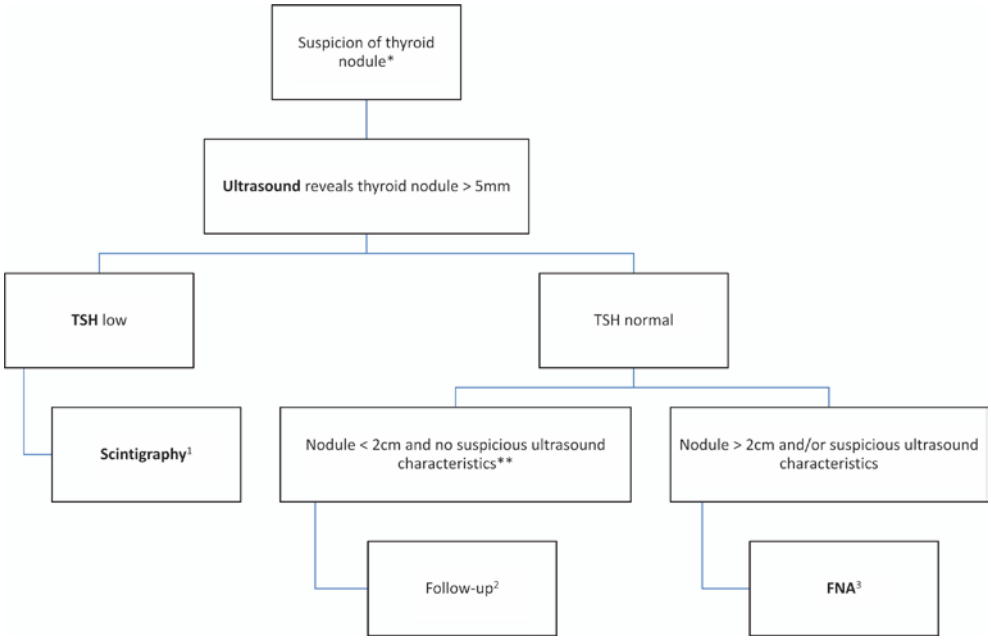


Fig. 15.4 Algorithm of the evaluation of nodular goiter patients. *Suspicion is based either on palpation or on clinical signs suggesting goiter or on previous imaging study. **Suspicious ultrasound characteristics involve (deep) hypoechogenicity, microcalcifications, irregular borders, taller-than-wide shape, pathological adenopathy, and suspicion of extrathyroidal spread. Average distribution of patients on first thyroid examination: 3–5% ([1]), 20–30% ([2]), 70–80% ([3])

have to add the fact though that this is true only under ideal conditions, i.e., when the US is performed by the clinician and FNA is available whenever necessary and FNA is performed by an experienced cytopathologist. Practice shows that if the clinician does not perform the US himself or there is a problem with FNA, often other, otherwise unnecessary examinations will be requested. We have summarized those conditions in Table 15.1 in which we require other diagnostic tests.

What are the major features of thyroid ultrasound examination?

US is the basis of the diagnosis of TN and guides further diagnostic steps. Thyroid US is able to detect discrete lesions smaller than 1 mm in maximal diameter. This sensitivity clearly exceeds all other imaging studies and had inevitably led to a poor specificity regarding not only malignant tumors but even the diagnosis of pathological nodules. We have no objective tools to separate discrete lesions which are not pathological nodules from those that are.

Thyroid US has a crucial role in all three indications of surgery. In autonomously functioning adenomas, the role of US is to detect the nodule. US is the only diagnostic test which is able to measure both the size of the nodule and often more importantly the size of the nodular lobe. Therefore, US has a decisive role in the surgical indication of goiters causing compression signs. Measuring the nodule(s) and the thyroid lobes is the basis for the follow-up of those patients who do not require operation at an actual examination but can be candidates for surgery later in their lifetime, if their thyroids grow. An US report that does not include the three diameters of the nodule(s) and diameters of the thyroid lobes is not suitable for this purpose.

There is a well-established role of US in guiding FNA, and it is expected that sampling should be US-guided. While in the last decade of the twentieth century, the guiding principle was to recognize all malignant

Table 15.1 Diagnostic tests to evaluate a patient with thyroid nodule

	When to perform?	How often is performed at first examination?
Ultrasound	Always	100%
TSH	Always	100%
Aspiration cytology		
Solid nodules >2 cm	Always	70–80%
Nodules >1 cm presenting suspicious ultrasound characteristics	Always	
Nodules between 0.5 and 1.0 cm presenting suspicious ultrasound characteristics	Should be considered	
Nodules without suspicious signs between 1 and 2 cm	Can be considered	
Scintigraphy	Thyroid nodule >1 cm and low TSH	3–5%
Neck and upper mediastinal CT	The lower pole of the thyroid cannot be visualized on ultrasound	1%
Tracheal X-ray	Suspicion of tracheal compression	1–3%
Serum calcitonin	For the slightest suspicion of medullary carcinoma	< 1%

thyroid lesions, the trends in the last decade, the principle has been changing, with an increasing effort to avoid FNA for benign thyroid lesions. Although there are quite a few features that can be used to find a statistically significant difference in the US presentation of benign and malignant nodules (see Figs. 15.1, 15.2, and 15.3), several things are always worth considering. Firstly, these characteristics have a great role in papillary thyroid cancers but fail in the recognition of follicular carcinomas. The latter is more prevalent in iodine-deficient countries compared with iodine-replete areas. Secondly, there is no biological standard regarding the most suspicious characteristics, and therefore the interobserver agreement ranges only from fair to moderate in the judgment of these features.

In order to come to a conclusion based on these features, it inevitably leads to some of the malignancies not being recognized. We can minimize the risk to overlook clinically relevant malignancies, but the risk will be never zero, especially in the case of follicular carcinomas. There is no universal cost-benefit calculation; this varies greatly from country to country. The published guidelines reflect the economical and healthcare conditions of rich countries which, additionally, are iodine-replete countries. Finally, while we make a tremendous effort to reduce cytological demand, it may be even more important to reduce the rate of unnecessary US examinations.

A rationally composed US report has great importance (see ▶ Box 15.1). Archiving the video taken during the US examination can be a significant help in terms of both a surgery and the comparison required for subsequent examinations and quality assurance. Capturing some images for these roles cannot fulfill these requirements.

Box 15.1 Essential Elements of Thyroid Ultrasound Report

The thyroid gland as a whole
- Three diameters of the lobes
- Basic echo structure
- Substernal spread if present

Discrete lesions >1 cm and if present suspicious characteristics >0.5 cm
- Three diameters
- Location within the thyroid
- Basic echo structure
- Suspicious characteristics if present

Lymph nodes in the neck should be evaluated if the thyroid has suspicious lesions.

What is the TIRADS classification?

Thyroid imaging reporting and data systems have been published by all important thyroid associations in the last several years. They categorize thyroid nodules based on the risk of malignancy and serve both for comparison of results among different evaluation groups and for indication on FNA (see ▶ Box 15.2).

Box 15.2 Some Considerations about the TIRADS Systems
- There are at least ten different systems including those of respected thyroid associations. There are small but significant differences among them – the systems are not interchangeable.
- The categorization is based on the composition (solid or cystic) and the presence or lack of suspicious ultrasound signs: The higher the category (score), the greater the likelihood of malignancy.
- The individual TIRADS is very good basis to compare the results of different evaluation groups.
- All TIRADS have a proposition on cytology based on the TIRADS score and on the size of the lesion. TIRADS score would influence our decision on cytology for nodules between 1 and 2 (2.5) cm. In smaller or larger nodules, the size alone decides the FNA indication.
- Regarding the suggestion on FNA indication, currently we do not have enough data to follow up these proposals in every patient.
- TIRADS is an excellent tool to recognize papillary and medullary carcinomas >1 cm.
- However, endocrinologists are not universally convinced to completely stop recognizing and thus treating subcentimeter thyroid carcinomas as TIRADS suggest.
- Moreover, by using the TIRADS for FNA indication, about half of follicular cancers would only be recognized when they grow larger than 2 cm.

What is the role of aspiration cytology?

FNA is the key to distinguish between benign and malignant thyroid lesions. For indication of FNA, see ◘ Table 15.1. This is a test that is easy to perform and also an inconvenience for the patient by being a blood test. On the other hand, the thyroid gland is one of the most difficult organs because general cytological signs suggesting the presence of a tumor (e.g., atypia, pleomorphism) are much less useful in the thyroid gland than in other organs because hormonal influences and thyroiditis might have greater impact on the presentation of thyroid cells than malignant transformation. As the main limitation, FNA is not able to discriminate between the most frequent thyroid tumor, the follicular adenoma, and its malignant counterpart, the follicular carcinoma.

As a consequence of the abovementioned obstacles, with a very good sensitivity (95–98%), the specificity and positive predictive value of the method is around 60% for a highly experienced thyroid cytopathologist.

Table 15.2 Comparison of cytological reporting systems

Cytological pattern	Bethesda system	Traditional system	UK Royal College of Pathologists
Nondiagnostic	I. Nondiagnostic	Nondiagnostic	Nondiagnostic
Benign	II. Benign	Benign	Benign
Some borderline patterns	III. Atypia or follicular lesion of unknown significance	Suspicion of malignancy	(Suspicion of) follicular neoplasm
			Suspicion of other thyroid cancer
(Suspicion of) follicular neoplasm	IV. (Suspicion of) follicular neoplasm		(Suspicion of) follicular neoplasm
Suspicion of other thyroid cancer	V. Suspicion of other thyroid cancer		Suspicion of other thyroid cancer
Malignant	VI. Malignant	Malignant	Malignant

What kind of classification systems are used for cytology?

Although the Bethesda system became very popular in the last 15 years, older and more established reporting systems can also be used (see Table 15.2). The former has the advantage first of all for less experienced cytopathologists, because with the introduction of category III (atypia or follicular proliferation of unknown significance), we are not forced to make decisions beyond our capabilities and/or beyond the limitations of the technique for certain patterns. Irrespectively of the reporting system used, the cytological finding should be expected to be clear and suitable for deciding what to do next. While the Bethesda system seems to lead to a better communication among cytopathologists and clinicians, paradoxically, the introduction of Bethesda system has further strengthened a traditional and occasionally not very efficient approach: Members of the evaluation teams communicate only *after they have concluded their reports*. This is in striking contrast with the histopathology: A histopathologist is aware of all clinical and radiological findings, which may have influenced her/his pathological report. Such approach in cytology, i.e., the *consideration of US features* ***after*** *the FNA diagnosis*, might have an even more influential role.

When to perform thyroid scintigraphy?

The role and therefore the use of scintigraphy have substantially decreased by introducing FNA and US in the evaluation. Thyroid scintigraphy (^{99m}Technetium (Tc) pertechnetate or ^{123}I) must be performed in patients who would be candidates for radioiodine therapy, i.e., in those with undetectable TSH level and nodule >1 cm otherwise not requiring surgery (Fig. 15.5). Thyroid scintigraphy might have a role in the case of euthyroid patients in whom FNA raises the suspicion of a follicular tumor: By detecting autonomously functioning adenoma, the patient can avoid surgery. These are those situations in which scintigraphy influenced the decision if all other circumstances of the evaluation are ideal – including the provision of regular follow-up examinations, as well.

How can molecular biology be used in the evaluation of patients with thyroid nodules?

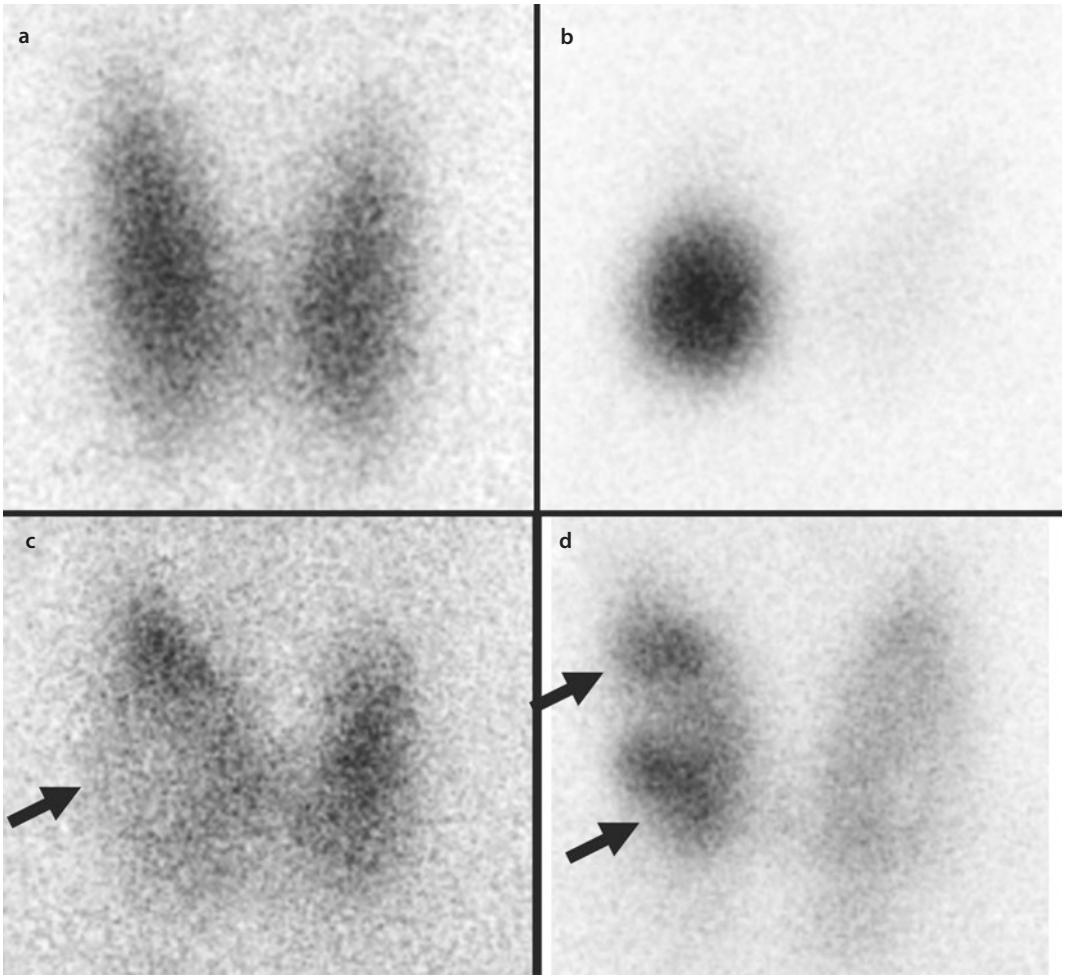


Fig. 15.5 Thyroid scintigraphy (^{99m}Tc pertechnetate) imaging of thyroid nodules. **a**, normal thyroid; **b**, a hot nodule in the right lobe, with the rest of the thyroid suppressed (toxic adenoma); **c**, a cold nodule in the right lobe; and **d**, multiple nodules in the right lobe. The relevance of cold nodules (decreased isotope uptake) has been greatly reduced nowadays, as malignancy is judged primarily by ultrasound and cytology and cold nodules are frequent in iodine-poor areas. Courtesy of Zsolt Varga MD, Chair of Nuclear Medicine, Medical Imaging Centre, Semmelweis University

While these techniques have a constantly increasing role in the prognosis of malignant thyroid tumors, currently they have limited role in the diagnosis and differential diagnostics of TN. One of the major concerns in the evaluation of TN is the lack of preoperative tools in discrimination of benign and malignant follicular tumors. The issue is much more complex as there is a significant difference in the histological separation of follicular adenoma and follicular carcinoma even among highly experienced physicians. Novel molecular techniques including mutation analysis of genes involved in thyroid cancer pathogenesis (e.g., *RAS*, *BRAF*, *PTEN*, *TERT*, *RET*/*PTC*), molecular classification based on mRNA (messenger RNA) expression (transcriptome), and microRNA expression analysis show promising results in the differentiation of benign and malignant thyroid tumors.

What are the basic considerations about thyroid surgery?

Table 15.3 Indications of definitive therapy in thyroid nodules

	Preferred therapy
Absolute indications	
Autonomously functioning adenoma with a TSH <0.1 mIU/L	Radioiodine
Suspicious or malignant cytology	Surgery
Compression sign caused by the goiter	Surgery
Relative indications	
Follicular tumor <2 cm without cytological atypia and without any suspicious clinical or ultrasound findings	Surgery
Relapsing thyroid cyst >2–2.5 cm	Ethanol sclerotherapy
Clinical suspicion of malignancy by experienced thyroidologist	Surgery
Wish of the patient	Surgery

The accepted methods of surgery are (near) total lobectomy or (near) total thyroidectomy. The traditional subtotal resection is not accepted as the risk of having to operate on the same lobe again in the event of a recurrent nodule must be ruled out. In the case of an experienced thyroid surgeon, the risk of both permanent recurrent nerve damage and permanent hypoparathyroidism is less than 1% after the first surgical procedures, and it is ten times higher if the patient has to have repeated surgery on the same lobe.

What are the indications for surgery or nonsurgical treatment?

The indications of a definitive treatment are enlisted in Table 15.3. These states in detail are the following:

(i) *Low TSH level*

It is quite clear that persistently undetectable TSH levels, i.e., subclinical (normal FT4/FT3 levels with undetectable TSH) or overt (elevated FT4 and/or FT3 levels) hyperthyroidism, are cardiological risk factors and therefore require definitive therapy. There is a gray zone when the TSH is detectable but below the lower limit. This can coexist with nonautonomously functioning nodules in a person with either an otherwise healthy thyroid gland or an autoimmune thyroid disease. Subsequent follow-up examinations in these borderline cases will decide what to do exactly.

(ii) *Surgical indication based on the results of FNA*

There is no doubt that a patient with suspicious (Bethesda V) or malignant (Bethesda VI) FNA report requires surgical intervention. The issue is the follicular proliferation, categorized either as Bethesda III (follicular lesion) or Bethesda IV (follicular tumor or suspicion of follicular tumor). In these patients we have to consider other factors as well, including the size and the US presentation of the lesion and the affected lobe and also the age and wish of the patient. Hopefully, molecular techniques will add some new insights to this issue in the near future.

It is very important that there is no worldwide uniform cancer incidence in these two categories. These incidences have to be determined in each evaluation group. In such cases, regular US and FNA monitoring of the patient may be considered instead of surgery.

(iii) *Compression caused by enlargement of the thyroid gland*

While there is little probability for uncertainty in the case of low TSH and suspicious FNA, the third reason for surgery can be determined with much more uncertainty. From a practical point of view, it is very important that it is not the size of the nodule but the size of the nodular lobe that determines whether the nodule causes any compression symptoms (see

Fig. 15.2). There is a close relationship between thyroid size and body weight, and the location of the thyroid has also a great influence. The lower the thyroid gland, the smaller the enlargement can cause compression and vice versa. It is clear that the patient's age significantly influences the decision, as well. The prognosis and therefore our proposal are different in a significant but not yet surgical case at age 20 and age 80. We also need to mention the important fact that a neck complaint of compression may not be caused by a (thyroid) disease.

What kind of other indications for definitive therapy can be established?

The *patient's wish* is the most important that has to be taken into account when the reasons above do not apply to the case. If the nodule is visible and esthetically disturbs the patient, it must be accepted that the patient wants to have surgery. A significant proportion of patients have difficulty tolerating the awareness that there is a so-called abnormal, albeit invisible, lesion in their thyroid gland. In that case, it needs to be explained even more thoroughly to the patient that the risk of having surgery is clearly greater than if it is not done.

Similarly, it is not uncommon for a *physician experienced in the thyroid gland to believe that a tumor may exist despite a negative FNA finding*. This happens in two scenarios. One is when there is data suggesting the possibility of a tumor: a suspicious palpation finding, vocal cord paralysis unexplained by other reasons, a rapid growth of a solid nodule, and a nodule that appears particularly suspicious on an US.

The other situation is encountered when FNA is repeatedly nondiagnostic for a solid nodule. 5–10% of all cytological examinations fall into this category even for highly experienced teams.

A special situation is for *benign cysts that recur* even in the case of repeated aspiration, which can be treated by alcohol treatment with very good results. However, it must be taken into account that alcoholic treatment as well as surgery in the case of cysts that do not cause complaints and do not exceed 2–2.5 cm can rarely be professionally justified.

What is the role of radioiodine treatment in the management of thyroid nodules?

Radioiodine therapy (RAI) is the preferred treatment of autonomously functioning autonomous adenomas either solitary or multifocal when the patient became clinically or subclinically hyperthyroid. RAI of euthyroid patients is not justified except for large autonomous adenomas because such patients frequently remain euthyroid even for their entire lifetime. The gray zone is the subnormal TSH, i.e., when TSH is detectable but it is below the normal range: RAI should be considered if the thyroid worsens the patient's cardiac status. Large-dose RAI is also used for decreasing large, nontoxic multinodular goiters when surgery is contraindicated.

About nonsurgical therapies and their role in the treatment of thyroid nodule

Percutaneous ethanol sclerotherapy, thermal ablation with radiofrequency or laser, microwave ablation, and high-intensity focused US are the possible alternatives for surgery. In contrast with other alternatives, ethanol sclerotherapy is very cheap and easy-to-perform and is the only modality in which we have gained long-term (>10 years) follow-up data on the efficiency. It has a well-established role in recurrent thyroid cysts. Any of the nonsurgical methods might have great role in special circumstances by decreasing the size of a benign nodule at least temporarily. Patients with high risk of anesthesia or surgical complications (recurrent nodules) and pregnant women are the main candidates. We have to consider in other patients that the risk of thyroid surgery is very low, and surgery is much more efficient than any of the alternatives. Moreover, it is not

justified to treat a patient without surgical indication with nonsurgical interventions.

What to do in patients who do not need definitive treatment?

Because TN nodule cannot be treated with drugs, the fundamental question is whether any of the conditions described in detail earlier will develop that will require surgery later in the patient's lifetime. This is almost always due to the growth of the lobe containing nodule(s). Repeated US and TSH in 1 to 3 years is the usual approach in euthyroid patients. The smaller the nodule, the longer the interval of follow-up examination. We did not anticipate that a benign nodule is able to become malignant; however, we have to consider the 5–10% false negative rate of FNA. Therefore, in nodules which increase by more than 30% in volume, FNA should be repeated. The bases of the follow-up are the size of the nodular lobe and that of the nodule(s). That is why it is crucial to give the three diameters of them at the first and subsequent US examinations.

Tips

The reader is advised to read the chapters on hypothyroidism and Hashimoto's thyroiditis (▶ Chap. 11), Graves' disease (▶ Chap. 12), and differentiated thyroid cancer (▶ Chap. 18).

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Conclusions

- Those who have the possibility of a nodular goiter should be examined on the basis of palpation, neck complaints, or patient history. US screening is not justified as a starting point as that would inevitably place an unmanageable burden on the examination system and as case study 1 proves it: US screening occasionally leads to unnecessary surgeries.
- The US examiner has a pivotal role in managing patients with TN. It is in the interest of the patient and the evaluation system to ensure a complete examination with as little load and appearance as possible. The key to this is for the clinician to perform both the US examination and the US-guided sampling. It must be ensured that the cytological analysis is performed by a cytologist experienced in thyroid cases.
- The most common cause of surgery is not the size of a nodule but the enlargement of the lobe containing the nodule (see case study 2). Accordingly, there is no more important data in the US report than the size of the lobes.
- Thyroid diseases, including more than 80% of thyroid carcinomas, only exceptionally shorten life expectancy or lead to a permanent decrease in quality of life. A thyroidologist is aware of these facts but the patients are not. One of the most important duties of the endocrinologist is to inform patients about the very good news.

Suggested Reading

1. Cheung K, Roman SA, Wang TS, Walker HD, Sosa JA. Calcitonin measurement in the evaluation of thyroid nodules in the United States: a cost-effectiveness and decision analysis. J Clin Endocrinol Metab. 2008;93:2173–80. https://doi.org/10.1210/jc.2007-2496.
2. Cibas ES, Ali SZ, Conference NCITFSotS. The Bethesda system for reporting thyroid cytopathology. Am J Clin Pathol. 2009;132(5):658–65. https://doi.org/10.1309/AJCPPHLWMI3JV4LA.
3. Gharib H, Hegedûs L, Pacella CM. Clinical review: nonsurgical, image-guided, minimally invasive therapy for thyroid nodules. J Clin Endocrinol Metab. 2013;98:3949–57. https://doi.org/10.1210/jc.2013-1806.
4. Gharib H, Papini E, Garber JR, Duick DS, Harrell RM, Hegedüs L, Paschke R, Valcavi R, Vitti P. American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi Medical guidelines for clinical practice for the diagnosis and man-

agement of thyroid nodules – 2016 update. Endocr Pract. 2016;22:622–39. https://doi.org/10.4158/EP161208.GL.

5. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26:1–133. https://doi.org/10.1089/thy.2015.0020.
6. Machens A, Holzhausen H-J, Dralle H. The prognostic value of primary tumor size in papillary and follicular thyroid carcinoma. A comparative analysis. Cancer. 2005;103:2269–073. https://doi.org/10.1002/cncr.21055.
7. Mauriello C, Marte G, Canfora A, Napolitano S, Pezzolla A, Gambardella C, Tartaglia E, Lanza M, Candela G. Bilateral benign multinodular goiter: what is the adequate surgical therapy? A review of literature. Int J Surg. 2016;28(Suppl 1):7–12. https://doi.org/10.1016/j.ijsu.2015.12.041.
8. Nikiforov YE. Molecular diagnostics of thyroid tumors. Arch Pathol Lab Med. 2011;135(5):569–77. https://doi.org/10.1043/2010-0664-RAIR.1.
9. Rosai J, DeLellis RA, Carcangiu ML, Frable WJ, Tallini G. (2015) Tumors of the thyroid and parathyroid glands. AFIP Atlas of Tumor Pathology: Series 4: American Registry of Pathology.
10. Russ G, Bonnema SJ, Erdogan MF, Durante C, Ngu R, Leenhardt L. European Thyroid Association guidelines for ultrasound malignancy risk stratification of thyroid nodules in adults: the EU-TIRADS. Eur Thyroid J. 2017;6:225–37. https://doi.org/10.1159/000478927.
11. Shin JH, Baek JH, Chung J, Ha EJ, Kim JH, Lee YH, Lim HK, Moon WJ, Na DG, Park JS, Choi YJ, Hahn SY, Jeon SJ, Jung SL, Kim DW, Kim EK, Kwak JY, Lee CY, Lee HJ, Lee JH, Lee JH, Lee KH, Park SW, Sung JY, Korean Society of Thyroid Radiology (KSThR) and Korean Society of Radiology. Ultrasonography diagnosis and imaging-based management of thyroid nodules: revised Korean Society of Thyroid Radiology consensus statement and recommendations. Korean J Radiol. 2016;17:370–95. https://doi.org/10.3348/kjr.2016.17.3.370.
12. Tessler FN, Middleton WD, Grant EG, Hoang JK, Berland LL, Teefey SA, Cronan JJ, Beland MD, Desser TS, Frates MC, Hammers LW, Hamper UM, Langer JE, Reading CC, Scoutt LM, Stavros AT. ACR Thyroid Imaging, Reporting and Data System (TI-RADS): white paper of the ACR TI-RADS Committee. J Am Coll Radiol. 2017;14:587–95. https://doi.org/10.1016/j.jacr.2017.01.046.
13. Tuttle M, Morris LF, Haugen B, Shah J, Sosa JA, Rohren E, Subramaniam RM, Hunt JL, Perrier ND. Thyroid differentiated and anaplastic carcinoma. In: Amin MB, Edge SB, Greene F, Byrd D, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley J, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM, Meyer LR, editors. AJCC cancer staging manual. 8th ed. New York: Springer International Publishing; 2017.
14. www.thyroidmanager.org. Endocrine Education, Inc., Chicago.
15. www.thyrosite.com. Solymosi T (ed), MEDI-CITO, Hungary. doi: 10.24390.

Subacute (de Quervain's) Thyroiditis

Peter Reismann

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_16

Opening

In this chapter, a relatively rare thyroid disorder will be discussed. Subacute thyroiditis is a transient inflammation of the gland caused by a "mimicry" mechanism after a viral infection. Typical symptoms, ultrasound features and the clinical course can aid in the diagnosis. The thyroiditis comes along with a functional disorder, thyrotoxicosis in the beginning and later on transient or definite subclinical/overt hypothyroidism or full recovery. Supportive medication and transient immunosuppressive therapy are the treatment options.

Having read this chapter, the reader will be able to diagnose and treat subacute thyroiditis.

Definition of the Disease

de Quervain's subacute thyroiditis is a subtype of the thyroid inflammatory diseases. It has some synonyms, as subacute (granulomatous) thyroiditis and giant cell thyroiditis. This is a typically painful, self-limited thyroiditis associated with various thyroid functions. In the beginning, the inflammation destroys the structure of one part of the thyroid gland with uncontrolled increase of blood fT_4 concentration resulting in a transient thyrotoxicosis. Restoration of the structure is associated with the underproduction of thyroid hormones clinically appearing as subclinical or overt hypothyroidism.

Aetiology: Subacute thyroiditis typically occurs a few weeks after an upper respiratory track viral infection or sore throat. There is a higher incidence in the late spring-early summer and autumn seasons. Some epidemiological studies showed an association between subacute thyroiditis and some enteroviruses, such as echovirus and Coxsackie A and B virus.

The thyroid inflammation is thought to be the result of cytolytic T-cell recognition of viral or similar antigens (virus-like particles: mimicry) present in follicular epithelium. The follicles are often infiltrated, resulting in disrupted basement membrane and rupture of the follicles. This leads to the uncontrolled outflow of prepared and stored hormones (mainly fT4) into the circulation resulting in a transient thyrotoxicosis.

Epidemiology: The typical appearance is between the ages of 40 and 50. de Quervain's thyroiditis is more frequent in females (female/male ratio is about 4:1). According to data from the United States, its incidence can be around 12/100,000/year.

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Case Report

A 43-year-old female patient was admitted to the emergency department because of intolerable neck pain. Her previous medical history was negative. No thyroid disease was known. She complained about increasing pain in her neck radiating to the jaw-ears. The neck pain became worse by swallowing or turning the head in the last 10 days. A few days prior, she was subfebrile. Her further complaints were palpitation, irritability, muscle weakness and sleep disturbance. With patient's recent history, she mentioned she has had a sore throat for a month ago, and a local antiseptic has been given by her general practitioner.

Physical examination revealed a goitre of the thyroid, which was very painful upon examination and even more painful by soft pressure on the thyroid. No nodule in the thyroid was palpable; some minor, tender lymph nodes were detectable in the neck area. Body temperature was 36.9 °C, blood pressure 148/90 mmHg, pulse 108/min and sO2 99%.

Which pieces of information are important?

Pain in the neck area, palpable lymph nodes and subfebrility are obvious signs of an inflammatory process in the affected region. Palpitation, irritability and sleep disturbance can refer to mild thyrotoxicosis.

What are the necessary examinations?

A full HEENT (head, eyes, ears, nose and throat) examination is needed to rule out any other causes of neck pain.

Laboratory testing to detect the inflammation severity and examine thyroid function is also needed.

Ultrasound of the neck is very important, which can support the diagnosis.

In non-obvious cases, fine-needle aspiration cytology can secure the diagnosis.

What kind of laboratory tests are needed?

To detect the inflammation, erythrocyte sedimentation rate, C-reactive protein and blood count are enough. For thyroid function evaluation, TSH and fT4 (and fT3) are mandatory. In many cases, the elevation of serum thyroglobulin is a typical marker for destruction of the gland. Autoantibodies, such as aTPO (anti-thyroid peroxidase) or aTG (anti-thyroglobulin) and TRab (thyroid receptor antibody), are usually normal. A slight and transient increase of aTPO during the disease course can be detected, but this is not related to Hashimoto's thyroiditis.

Our patient's initial laboratory results

ESR:	72 mm/h (normal 1–20),
CRP:	26 mg/L (normal <5),
TSH:	0,138 mU/L (normal 0.4–4.5),
fT4:	16,4 pmol/L (normal12–22)
Thyroglobulin	456.4 ng/mL (normal 3–80)

What are the typical features of de Quervain thyroiditis by imaging?

Thyroid ultrasound

The typical sonographic appearance is poorly defined, usually hypoechogenic regions are seen with decreased vascularity in the affected area. Often it appears in one lobe in the beginning, and during the disease course, it can change sides and appear in the other lobe as well. The rest of the thyroid remains unchanged (Fig. 16.1). During the examination, the pressure of the ultrasound probe on the thyroid region is often painful for the patient.

There is an improvement of the hypoechogenic region after treatment. However, in the long term, a size reduction of the thyroid gland is often observed.

Nuclear medicine

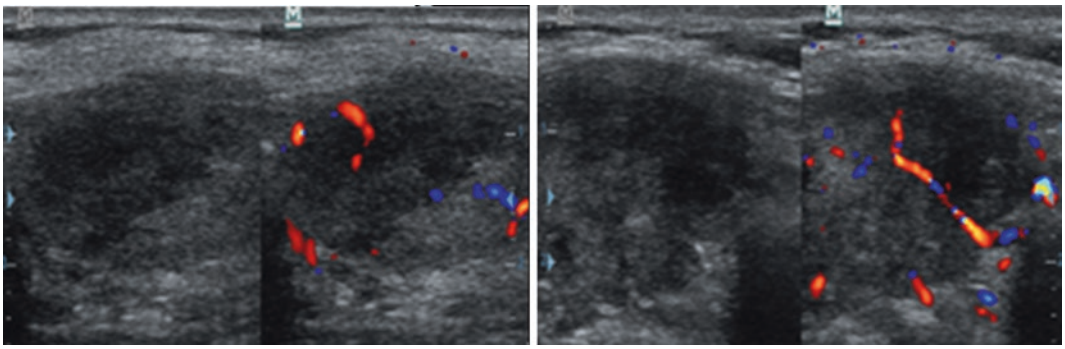

Fig. 16.1 Typical ultrasound features of subacute (de Quervain's) thyroiditis: areas with decreased echogenecity and vascularity with poorly defined borders

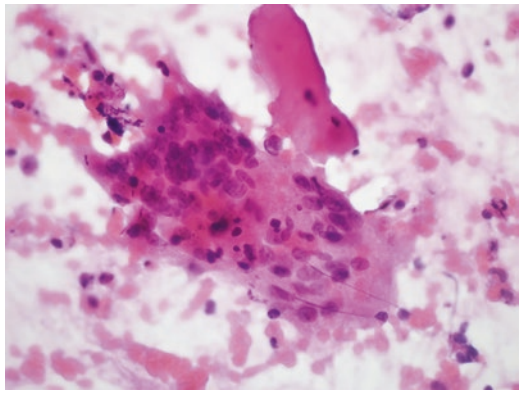

Fig. 16.2 Typical cytological appearance of de Quervain's thyroiditis on a smear of FNA (Courtesy of Eszter Szekely MD, 2nd Department of Pathology, Semmelweis University, Budapest)

Due to the destruction of the thyroid tissue, the typical occurrence is a low uptake on the thyroid scintigraphy (^{99m}Tc) scan.

What is the role of fine-needle aspiration biopsy (FNAB)?

If the diagnosis is not obvious, or the ultrasound features are ambiguous, aspiration cytology from the hypoechogenic region is recommended. On the smear, mainly follicular epithelial cells with degenerative changes arranged as honeycomb fragments, mixed inflammatory cells (lymphocytes, macrophages) and multinucleated giant cells are detectable (Fig. 16.2).

What is the typical disease course?

de Quervain's thyroiditis is a self-limited inflammatory disease of the thyroid. It has some phases over a period of weeks to months. At the beginning, excessive neck pain and mild thyrotoxicosis are the leading symptoms. Thereafter, the pain eases and the hyperthyroidism is followed by a transient euthyroid phase. After this, the local symptoms completely disappear, but a transition to hypothyroid function is observed. In many cases, a complete remission is expected with euthyroid function, but in several patients, chronic hypothyroidism remains as a long-term consequence.

What are the treatment options?

There are two key points in the treatment of de Quervain's thyroiditis. One is the anti-inflammatory treatment, and the other is the support of the dysfunction.

As an anti-inflammatory medication, high-dose salicylates or other NSAIDs (non-steroidal anti-inflammatory drugs) can be used for patients with mild or moderate disease. In advanced cases, the transient use of corticosteroids is recommended. Starting dose can be 20–24 mg methylprednisolone or 25–30 mg prednisolone a day, tapered over 3–4 weeks. In any of these treatment options, gastric ulcer prevention is warranted (H2-blocker or PPI). A marked improvement in neck pain is observed 1–2 days after initial treatment.

Thyrotoxicosis phase does not need anti-thyroid drugs, but in case of symptoms of palpitation, tachycardia or agitation, a beta-blocker, such as propranolol, can be started (dose 3x20 mg/day).

In the hypothyroid phase, one might need levothyroxine treatment, but observation in subclinical or mild form of hypothyroidism is also accepted.

If overt hypothyroidism lasts sustained, ultrasound shows marked reduction of the thyroid size with diffuse hypoechogenic appearance, long-term levothyroxine substitution is required.

Would thyrostatic drugs be anyway effective in de Quervain's thyroiditis?

As the transient thyrotoxicosis in de Quervain's thyroiditis is due to the destruction of the thyroid tissue, drugs inhibiting thyroid biosynthesis would be ineffective.

Follow-Up of the Case Presentation

The patient's clinical presentation, laboratory and ultrasound results gave an obvious diagnosis of de Quervain's thyroiditis. For treatment, acetylsalicylic acid 4x500 mg/day and propranolol 3x20 mg were given. After 1 week, the patient still complained of severe neck pain; therefore the medication was turned to methylprednisolone 24 mg, and acetylsalicylic acid was stopped. After 3 days of glucocorticoid administration, the patient reported a significant improvement of symptoms. Propranolol could be stopped in 2 weeks. Tapering the corticosteroid was made over 5 weeks.

Changes of laboratory values during follow-up are presented in ◘ Table 16.1.

As seen in the laboratory results, a transient hypothyroidism occurred, but the symptoms were mild, and therefore no levothyroxine therapy was given. A complete remission was detected after 8 months from disease onset.

◘ **Table 16.1** Laboratory values during the disease course

Date	ESR (normal 1–20 mm/h)	CRP (normal <5 mg/L)	TSH (normal 0.4–4.5 mIU/l)	fT4 (12–22 pmol/L)	Thyroglobulin (normal 3–80 ng/mL)
Beginning	72 mm/h	26 mg/L	0.138 mIU/L	16.4 pmol/L	
1 month later	68 mm/h	7,8 mg/L	0.007 mIU/L	25 pmol/L	238.7 ng/mL
3 months later	6 mm/h	1 mg/L	0.016 mIU/L	10.6 pmol/L	67.2 ng/mL
6 months later	11 mm/h	3 mg/L	16.4 mIU/L	11.3 pmol/L	
9 months later	13 mm/h	2 mg/l	3.9 mIU/L	16 pmol/L	

ESR erythrocyte sedimentation rate

What is the prognosis of subacute de Quervain's thyroiditis?

It is a self-limited disease returning to euthyroid state in a few months. Recurrence is uncommon (2%), while long-term hypothyroidism is expected in 5–10%.

What kinds of other diseases should be ruled out?

As differential diagnosis, there are several diseases with neck pain, while thyrotoxicosis has limited reasons, shown in ◘ Table 16.2.

What kinds of other forms of thyroiditis are known?

Acute suppurative thyroiditis (infectious thyroiditis) is rare, but severe, and is caused by the bacterial infection of the thyroid leading to abscess formation. Intensive neck pain and mass, fever and tenderness can be seen. Ultrasound and FNAC are needed for differential diagnosis. Treatment with antibiotics and often drainage are needed.

Chronic forms of thyroiditis include Hashimoto's thyroiditis presented in ▶ Chap. 11, amiodarone-induced thyroiditis (▶ Chap. 17) and Riedel's thyroiditis.

Table 16.2 Differential diagnosis of de Quervain's subacute thyroiditis

Differential diagnosis of neck pain	Differential diagnosis of thyrotoxicosis
Dental pain	Graves' disease
Pharyngitis	Initial phase of Hashimoto's thyroiditis
Otitis	Drug-induced thyroiditis (e.g. amiodarone)
Abscess	Radiation thyroiditis
GERD	Iodine-intoxication (CT contrast agent)
Suppurative thyroiditis	Toxic nodular goitre

GERD gastroesophageal reflux disease

Riedel's thyroiditis is a rare fibroinflammatory disease (incidence about 1/100,000/year) characterized by an invasive fibrosis of the thyroid that can be linked to fibrosis in other organs. It belongs to the group of IgG4-related diseases (interstitial pneumonia, autoimmune pancreatitis, orbital pseudotumor). Riedel's thyroiditis eventually results in an enlarged hard and firm thyroid, which can cause compression symptoms (e.g. dysphagia). Patients are mostly euthyroid, but hypothyroidism can also be observed, and if the parathyroid glands are infiltrated, hypoparathyroidism might also develop. Whereas the fibrotic and IgG4-related forms of Hashimoto's thyroiditis (▶ Chap. 11) are always confined to the thyroid gland, Riedel's thyroiditis usually spreads beyond the thyroid capsule. Surgery is needed in patients with compression symptoms, but it is usually difficult, and the rate of complications can be high due to the extensive fibrosis. Immunosuppressive treatment with glucocorticoids is mostly used, but trials with tamoxifen and rituximab (anti-CD20 antibody) have also been reported.

Pregnancy-related postpartum thyroiditis is a form of Hashimoto's thyroiditis (▶ Chap. 11) discussed in ▶ Chap. 21.

Tips

The reader is advised to read the chapters on thyroid nodule and multinodular goitre (▶ Chap. 15), hypothyroidism and Hashimoto's thyroiditis (▶ Chap. 11) and Graves' disease (▶ Chap. 12). Postpartum thyroiditis is discussed in ▶ Chap. 21.

Take-Home Messages

- de Quervain's subacute thyroiditis is a self-limited, inflammatory thyroid disorder with functional changes from mild thyrotoxicosis to transient hypothyroidism.
- The most typical appearance is the severe neck pain at the disease onset.
- Besides the clinical symptoms, laboratory and ultrasound findings are essential for the diagnosis.
- In mild cases, non-steroidal anti-inflammatory drugs (NSAIDs) and, in severe cases, transient corticosteroid medication are recommended.
- Thyrotoxicosis does not need antithyroid drugs, but overt hypothyroidism can be substituted with levothyroxine.

Suggested Reading

1. Benbassat CA, Olchovsky D, Tsvetov G, Shimon I. Subacute thyroiditis: clinical characteristics and treatment outcome in fifty-six consecutive patients diagnosed between 1999 and 2005. J Endocrinol Investig. 2007;30:631. https://doi.org/10.1007/BF03347442.
2. Desailloud R, Hober D. Viruses and thyroiditis: an update. Virol J. 2009;12(6):5. https://doi.org/10.1186/1743-422X-6-5.
3. Engkakul P, Mahachoklertwattana P, Poomthavorn P. Eponym: de Quervain thyroiditis. Eur J Pediatr. 2011;170(4):427–31. https://doi.org/10.1007/s00431-010-1306-4.

4. Falhammar H, Juhlin CC, Barner C, Catrina SB, Karefylakis C, Calissendorff J. Riedel's thyroiditis: clinical presentation, treatment and outcomes. Endocrine. 2018;60(1):185–92. https://doi.org/10.1007/s12020-018-1526-3.
5. Golden SH, Robinson KA, Saldanha I, Anton B, review LPWC. Prevalence and incidence of endocrine and metabolic disorders in the United States: a comprehensive review. J Clin Endocrinol Metab. 2009 Jun;94(6):1853–78. https://doi.org/10.1210/jc.2008-2291.
6. Lazarus JH. Silent thyroiditis and subacute thyroiditis. In: Braverman LE, Utiger RD, editors. The thyroid: a fundamental and clinical text. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 1996. p. 577.
7. Slatosky J, Shipton B, Wahba H. Thyroiditis: differential diagnosis and management. Am Fam Physician. 2000; 15;61(4):1047–52.
8. Tabasson A, Edens MA. De Quervain thyroiditis. Treasure Island: StatPearls Publishing; PMID: 3025322. Bookshelf ID: NBK526066
9. Vitti P, Rago T, Barbesino G, Chovato L. Thyroiditis: clinical aspects and diagnostic imaging. Rays. 1999;24(2):301–14.

Amiodarone-Induced Thyroiditis

Endre V. Nagy and Miklós Bodor

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_17

Opening

In this chapter, the reader will get acquainted with amiodarone-induced thyroid dysfunction, a side effect which may manifest itself as either hypothyroidism or, less often, hyperthyroidism.

Definition of the Disease

Amiodarone, a class III antiarrhythmic agent, is frequently used in the treatment and prevention of life-threatening, and long-term suppression of other, cardiac arrhythmias. Due to its high iodine content, it may cause either hypothyroidism (in 10% of those patients who are on continuous daily treatment) or, less frequently, hyperthyroidism. The mechanism is the induction of new onset, or worsening of preexisting thyroiditis. Amiodarone-induced hypothyroidism is easily corrected by daily levothyroxine intake. The treatment of amiodarone-induced hyperthyroidism is often a challenge, especially in those patients in whom amiodarone cannot be stopped because it is the only effective measure to prevent their life-threatening arrhythmias. The majority of amiodarone-induced hyperthyroidism cases are Type 1, the course of which is reminiscent of Graves' hyperthyroidism. Type 2 is rather self-limiting, resembling thyroiditis.

Case Presentation

A 58-year-old man has been on amiodarone for more than 8 months because of paroxysmal atrial fibrillation. Since then, the weekly 1 to 5 paroxysms have not returned, and regular sinus rhythm was repeatedly confirmed on 24 hours ECG monitoring. The amiodarone daily dose was one 200 mg tablet. In spite of good appetite, he lost 6 kg weight in the last 2 months and experienced heat intolerance. Heart rate was 68/min. The thyroid was mildly enlarged, nonnodular by palpation. In the tests ordered, the only remarkable values were the thyroid function tests: TSH 0.001 (normal 0.3–4.2 mIU/L), FT4 >100 (normal 12–22 pmol/L), and FT3 12 (normal 2.4–6.3 pmol/L). No anti-thyroid peroxidase, no anti-thyroglobulin, and no TSH receptor antibodies were present in the sera. On ultrasound, a normal-sized thyroid was seen, with normal echogenicity and mildly increased blood flow. No nodules.

Are there additional tests to perform?

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In a patient on amiodarone, in the absence of nodules, new-onset hyperthyroidism is amiodarone-induced. The next step is to decide whether Type 1 or Type 2 amiodarone hyperthyroidism is present. This is of paramount importance, as both the treatment and the prognosis are different (see below). The easiest way to make this distinction is ultrasound; in Type 2, the thyroid tissue is hypoechogenic (Table 17.1). Interleukin-6 (IL-6) is normal or mildly elevated in Type 1 but high in Type 2; this is a test which has become readily available with a short turnaround time in many laboratories during the COVID-19 era. Further, nuclear imaging with methoxyisobutylisonitrile (MIBI) may help to differentiate between the two types. ^{99m}Tc imaging, which is often used in thyroid diseases, is impeded by the iodine exposure, and there is no uptake by the thyroid.

In our case, Type 1 amiodarone hyperthyroidism was suspected based on the lack of hypoechogenicity on ultrasound and confirmed by the normal IL-6 level in the serum.

Table 17.1 The two types of amiodarone-induced hyperthyroidism

	Type 1	Type 2
Clinical presentation	Resembles Graves' hyperthyroidism	Resembles thyroiditis (painless)
Pathogenesis	Increased hormone synthesis	Uncontrolled hormone release due to destruction
Interleukin-6	Normal or mildly elevated	High
Hypoechogenicity on ultrasound	Absent	Present
Color Doppler ultrasound	Increased flow	Normal or decreased flow
MIBI[a] accumulation	Present	Absent
Treatment	Thionamides with or without potassium perchlorate	Glucocorticoids

[a] *MIBI* ^{99m}Tc-labeled methoxyisobutylisonitrile

Why is it important to identify the type of amiodarone hyperthyroidism? How is treatment different in the two types?

The course of Type 1 amiodarone hyperthyroidism resembles Graves' hyperthyroidism, while Type 2 is rather reminiscent of destructive thyroiditis. Treatment options and prognosis are different. In Type 1, there is no chance to control hyperthyroidism without the cessation of amiodarone treatment. Continuation or cessation has to be a shared decision with the cardiologist. As our patient had Type 1 amiodarone hyperthyroidism, amiodarone was stopped, and thiamazole (a thionamide-type anti-thyroid drug) in relatively high doses, i.e., 60 mg/day was started. Occasionally, potassium perchlorate (an inhibitor of iodine transport) up to 2000 mg/day has to be added, but was not required in our patient. Of note, there is a protracted response to thiamazole, and it takes 3 months or more until euthyroidism is achieved; thiamazole can be stopped after another 3 months.

What are the treatment choices, if, due to life-threatening arrhythmias, amiodarone cannot be stopped?

In amiodarone-dependent patients, thyroidectomy may be required. This is especially cumbersome as both the heart disease and hyperthyroidism increase the risk during surgery. Radioiodine is ineffective as the thyroid is filled with iodine and the uptake is low. In preparation for surgery, plasmapheresis may be considered.

The hormone results suggested very severe hyperthyroidism while signs and symptoms were rather mild. How is it possible?

This is typical with amiodarone hyperthyroidism: high hormone levels are accompanied with scanty signs. While serum hormone levels are high, there is only mild tissue-level hyperthyroidism due to the blocking effect of the amiodarone molecule both on the conversion of T4 to T3 and, at the thyroid hormone receptor, a consequence of the structure homology between thyroid hormones and amiodarone.

What would be the treatment if our patient had Type 2 amiodarone hyperthyroidism?

Type 2 responds well to a short course of oral corticosteroids, typically methylpred-

nisolone 32 mg per day, tapered over 6–8 weeks. Amiodarone may be continued, or reinstituted if has been stopped.

What happens if a patient in whom amiodarone treatment has been abandoned has to receive amiodarone again for unforeseen life-threatening arrhythmias?

In Type 1, recurrence of hyperthyroidism is usual. Amiodarone should be avoided or treatment kept at a minimum length. Preventive thyroidectomy may be required if amiodarone cannot be stopped. In Type 2, no recurrence can be expected and amiodarone may be re-initiated.

Can thiamazole and steroid be used combined, if, for some reason, it cannot be decided if the amiodarone hyperthyroidism is Type 1 or Type 2?

Yes, although it is not suggested

How is amiodarone hypothyroidism managed?

Up to 10% of patients regularly taking amiodarone develop amiodarone-induced hypothyroidism, which is reversible with the cessation of treatment. However, cessation is not required as daily levothyroxine supplementation, according to the management of hypothyroidism described in ▶ Chap. 11, can sustain euthyroidism.

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Tips

The reader is advised to read the preceding chapters on hypothyroidism and Hashimoto thyroiditis (▶ Chap. 11) and Graves' disease (▶ Chap. 12).

Take-Home Messages

- Amiodarone may induce hyperthyroidism or, more frequently, hypothyroidism.
- In patients on amiodarone, the TSH level needs to be checked at least once in every 3 months, even in the absence of clinical signs of thyroid dysfunction.
- The treatment of hyperthyroidism is different in Type 1 and Type 2 amiodarone-induced hyperthyroidism.
- Type 1 and Type 2 amiodarone-induced hyperthyroidism should be distinguished by ultrasound features and serum interleukin-6 levels.
- Type 1 amiodarone-induced hyperthyroidism resembles Graves' disease and is primarily treated by anti-thyroid drugs, whereas Type 2 is reminiscent of a destructive thyroiditis and is treated with glucocorticoids.
- Amiodarone-induced hypothyroidism requires levothyroxine treatment; the patient may continue on amiodarone.

Suggested Reading

1. Franklyn JA, Davis JR, Gammage MD, Littler WA, Ramsden DB, Sheppard MC. Amiodarone and thyroid hormone action. Clin Endocrinol (Oxf). 1985;22(3):257–64. https://doi.org/10.1111/j.1365-2265.1985.tb03238.x.
2. Ryan LE, Braverman LE, Cooper DS, Ladenson PW, Kloos RT. Can amiodarone be restarted after amiodarone-induced thyrotoxicosis? Thyroid. 2004;14(2):149–53. https://doi.org/10.1089/105072504322880391.
3. Trohman RG, Sharma PS, McAninch EA, Bianco AC. Amiodarone and thyroid physiology, pathophysiology, diagnosis and management. Trends Cardiovasc Med. 2019;29(5):285–95. https://doi.org/10.1016/j.tcm.2018.09.005.
4. Wang J, Zhang R. Evaluation of ^{99m}Tc-MIBI in thyroid gland imaging for the diagnosis of amiodarone-induced thyrotoxicosis. Br J Radiol. 2017;90:20160836. https://doi.org/10.1259/bjr.20160836.

Differentiated Thyroid Cancer

Emese Mezősi

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_18

Opening

In this chapter, differentiated thyroid cancer (DTC) is discussed focusing on the advanced-stage disease with emphasis on pitfalls in the risk classification, diagnostic workup, follow-up, and treatment.

Definition of the Disease

DTC contains the heterogeneous group of papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), and Hurthle cell thyroid cancer whose malignant potentials are distributed in a wide range. The incidence of DTC increases worldwide but varies considerably in different regions, ranging between 1.2 and 2.6/100,000 individuals in men and 2.0 and 3.8/100,000 in women. This increased incidence is mainly attributed to the more common detection of early-stage DTC. TNM (tumors, nodes, metastases) staging, risk classification, indications of radioiodine (RAI) treatment, evaluation of response to therapy, and TSH target ranges have been recently changed. The current (eighth edition) TNM classification system for differentiated thyroid cancer is shown in Table 18.1. The prognosis of early-stage disease is excellent, and the current American Thyroid Association (ATA) guidelines suggest less radical treatment and follow-up in these cases. However, 7–10% of DTC cases develop distant metastases, and two-thirds of these patients become RAI-refractory. The management of RAI-refractory patients has markedly developed currently with the availability of new treatment modalities. Despite these advances, there are uncertainties in the following fields: follow-up of patients with anti-thyroglobulin antibody (TgAb) positivity, the optimal imaging workup, definition of progressive disease, and initiation and cessation of targeted therapy in RAI-refractory metastatic DTC.

Table 18.1 TNM classification system for differentiated thyroid cancer (eighth edition)

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor size maximum 2 cm, limited to the thyroid
T1a	Tumor size maximum 1 cm, limited to the thyroid
T1b	Tumor size >1 cm up to a maximum of 2 cm, limited to the thyroid
T2	Tumor size >2 cm up to 4 cm, limited to the thyroid
T3	Tumor size >4 cm, limited to the thyroid, or any tumor with macroscopic extrathyroidal extension (musculus sternohyoideus, musculus sternothyroideus, musculus omohyoideus)
T3a	Tumor size >4 cm, limited to the thyroid
T3b	Any tumor with macroscopic extrathyroidal extension (m. sternohyoideus, m. sternothyroideus, m. omohyoideus)
T4a	Any tumor size with extrathyroidal extension beyond the thyroid capsule and invasion of subcutaneous soft tissue, larynx, trachea, esophagus, and/or recurrent laryngeal nerve
T4b	Any tumor size with invasion of prevertebral fascia, mediastinal vessels, or carotid artery
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases

Table 18.1 (continued)

N1	Regional lymph node metastases
N1a	Lymph node metastases unilateral in level VI or upper mediastinum
N1b	Metastases in other unilateral, bilateral, or contralateral cervical lymph nodes (level I, II, III, IV, and V) or retropharyngeal
Mx	Distant metastases not assessed
M0	No distant metastases
M1	Distant metastases

Patient age <55 years			
Stage I	Any T	Any N	M0
Stage II	Any T	Any N	M1
Patient age 55 years or older			
Stage I	T1a, T1b, T2	N0	M0
Stage II	T3	N0	M0
	T1, T2, T3	N1	M0
Stage III	T4a	Any N	M0
Stage IV/A	T4b	Any N	M0
Stage IV/B	Any T	Any N	M1

Case Presentation

In 2006, near total thyroidectomy was done in a 62-year-old female patient because fine-needle aspiration biopsy diagnosed PTC in the right lobe. Histology confirmed PTC (17 mm, minimal extrathyroidal extension (pT3 in AJCC/TNM seventh, pT1 in TNM eighth edition) without lymph node involvement. The patient was TgAb-positive (704 IU/ml, normal range <40 IU/ml, Elecsys® TG II assay, Roche). She received 2.5 GBq RAI treatment; post-therapeutic scintigraphy revealed only a remnant thyroid tissue. No decrease in the TgAb titer was found in the next 2 years – in 2008, rhTSH (recombinant human TSH)-stimulated RAI treatment was performed (3.7 GBq); no pathological RAI accumulation on SPECT-CT but multiple uncertain CT lesions in the calvaria were found; PET-CT was negative. The patient was treated by suppressive dose of levothyroxine and underwent regular follow-up visits. No change in the TgAb titer and negative US results were found until September 2015. In September 2015, a further rise of TgAb titer was measured (Fig. 18.1), and neck US showed a 15 mm pathological lymph node in neck region VI and an 8 mm in right region III–IV; FNAB confirmed metastasis of papillary cancer. In Nov 2015, percutaneous ethanol sclerotherapy (PEI) of the metastatic lymph node in region VI was done. Till February 2016, the size of the treated lymph node decreased to 11 mm, its vascularization disappeared, and no progression in other lymph nodes was observed. In July 2016, chest CT detected multiple pulmonary macronodular metastases and a 45 mm mass in the mediastinum. RAI therapy was performed with 3.7 GBq; SPECT-CT detected low RAI accumulation in the mediastinal mass

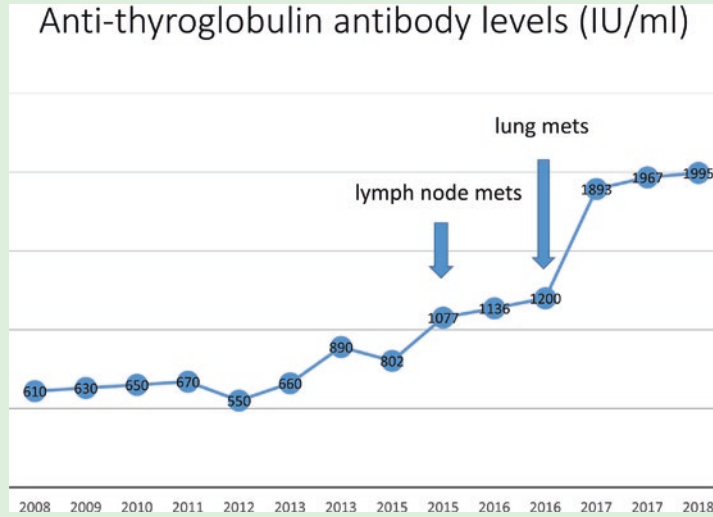

Fig. 18.1 Changes in the TgAb titers during follow-up of the presented case. The measurements were done by Elecsys® anti-TG assay, Roche (normal value <40 IU/ml). The time of diagnosis of lymph node and pulmonary metastases is shown by arrows (met metastasis)

and no uptake in the pulmonary metastases (Fig. 18.2). PET-CT demonstrated intensive FDG uptake in the metastases (Fig. 18.2). No tumor of other origin was found. Sorafenib treatment was started, but due to severe side effects (erythema, skin ulcers, hand-foot syndrome, alopecia, bad general condition), the patient finally refused this therapy. TSH suppression was maintained. In October 2019, she was still in good general condition, but chest CT detected a >20% increase in the diameter of one pulmonary metastasis, but all other lesions were stable, and the mediastinal mass decreased in size (from 45 to 27 mm). Slow progression was established, and the patient repeatedly refused systemic therapy.

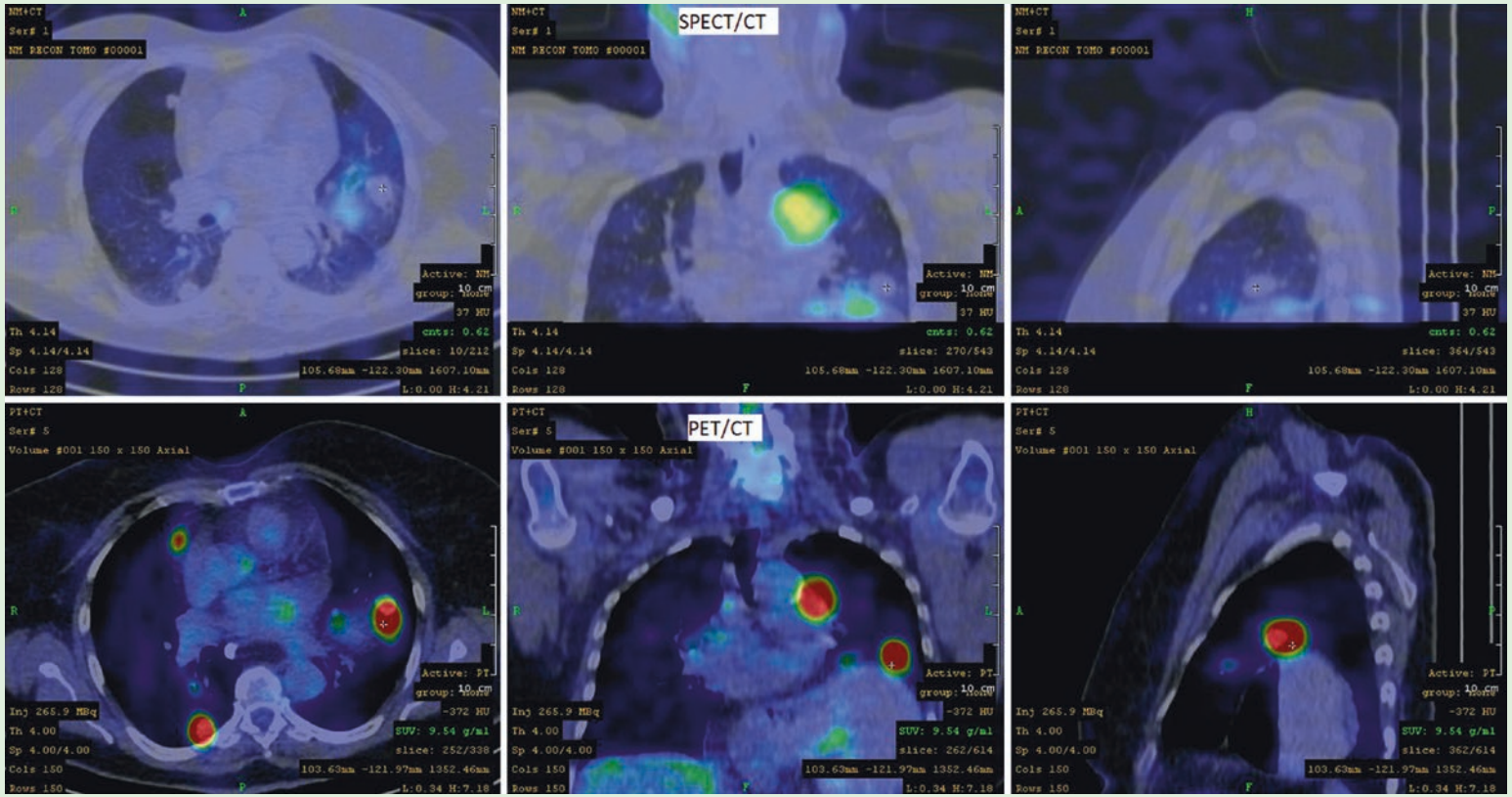

Fig. 18.2 SPECT-CT (upper panel) and PET-CT (lower panel) images of the patient after the third radioiodine treatment. SPECT-CT detected moderate RAI accumulation in the mediastinal mass and no uptake in the pulmonary metastases. PET-CT demonstrated intensive FDG uptake in the metastases. (By courtesy of Erzsebet Schmidt)

What are the main symptoms of DTC?

DTC is usually a palpable and painless mass discovered incidentally during physical examination or by the patient itself; the majority of patients is asymptomatic. Large tumors may cause cervical discomfort, dysphagia, or hoarseness (due to palsy of the recurrent laryngeal nerve). The differential diagnosis of thyroid nodules is discussed elsewhere (► Chap. 15). Cervical lymph node metastases may be the first symptoms, especially in young patients with PTC. The presence of distant metastases is uncommon at the time of diagnosis; it may occur in FTC and poorly differentiated thyroid cancer; the typical locations of distant metastases are the lungs and the bones.

Are there differences in the clinical behavior of papillary and follicular thyroid cancer?

The ratio of PTC/FTC is influenced by the iodine supply; FTC is more common in iodine-deficient countries. FTC may represent 30% of DTC in case of iodine deficiency, while its occurrence is only 6–12% of DTC in iodine-sufficient regions. PTC is usually not encompassed by a capsule, it may be multifocal, and the primary metastatic sites are the cervical lymph nodes. The development of distant metastases is <5% at the time of diagnosis. The typical FTC is a solid, solitary, and encapsulated tumor, and the presence of lymph node metastases is rarer than in PTC. Its prognosis is worse due to the more common distant metastases; however, if the tumor size is <2 cm, the presence of distant metastasis is exceptional.

What are the features of the Hurthle cell thyroid cancer?

Hurthle cell cancer has a more aggressive clinical course. Hurthle cells or oncocytes look differently than the follicular cells. They are bigger with a pink-staining cytoplasm. The major difference in the biological behavior of Hurthle-cell cancer compared to other types of DTC is that it cannot accumulate radioiodine due to the lack of expression of functional sodium-iodide symporter (NIS).

What are the therapeutic options for DTC?

The first-line treatment of DTC is surgery. The extent of surgery depends on the stage of disease. In case of tumors <1 cm without extrathyroidal extension and lymph node involvement, lobectomy is preferred. Based on the excellent prognosis of early-stage DTC, the ATA guideline suggested lobectomy or near total/total thyroidectomy in case of 1–4 cm tumors (pT1b, pT2). Near total/total thyroidectomy is recommended if the primary tumor is ≥4 cm, extrathyroidal extension is detected, and lymph node or distant metastases are diagnosed. Therapeutic regional lymph node dissection should be performed in cases with clinical evidence of central or lateral nodal metastases. Prophylactic central compartment lymph node dissection should be considered if the primary tumor is advanced (pT3 or pT4) or if the lateral neck lymph nodes are affected.

The purpose of radioiodine (RAI) treatment after thyroidectomy may be (i) the ablation of residual normal thyroid tissue; (ii) adjuvant therapy of subclinical micrometastatic disease; or (iii) treatment of clinically apparent residual or metastatic thyroid cancer. The risk of recurrence or persistent disease determines whether RAI treatment is required or not. RAI is routinely administered after total thyroidectomy in high-risk patients and in selected intermediate-risk patients; according to the ATA guideline, RAI therapy for remnant ablation is not routinely recommended in low-risk disease.

The third mainstay of treatment is the replacement of thyroid hormone.

How is RAI treatment performed?

RAI therapy is applied 4–6 weeks after near total/total thyroidectomy. It cannot be used if the surgical procedure was only

lobectomy. No disadvantage was found if the therapy was postponed up to half a year. Elevated TSH during RAI therapy is essential as TSH stimulates the RAI uptake. The preparation of patients should be done by levothyroxine withdrawal (thus inducing primary hypothyroidism) or by recombinant human TSH (rhTSH) stimulation, as at least 30 mIU/L TSH is required for effective treatment. The effect of RAI treatment is markedly decreased by iodine contamination; therefore CT with contrast material should be avoided before the administration of RAI. For remnant ablation, 1.1 GBq RAI (^{131}I) is recommended. Adjuvant therapy is performed by 3.7 GBq. The curative/palliative activity for residual or metastatic disease is 3.7–7.4 GBq. RAI treatment should be repeated in 6–12 months' time.

Whole-body scintigraphy and supplementary SPECT-CT images 3–6 days after RAI therapy are really useful for correct staging and risk stratification.

What is the role of TSH suppression in DTC management, and how should this be performed?

The target TSH range during levothyroxine therapy is determined based on the risk for recurrence. Low-risk patients after lobectomy may not need any therapy. Low-risk cases after thyroidectomy (w/wo RAI) without detectable thyroglobulin (Tg) are treated targeting normal TSH (0.5–2 mIU/L). The target TSH range in low-risk patients with detectable Tg and intermediate-risk cases is 0.1–0.5 mIU/L. Patients with high risk or persisting disease require suppressive dose of levothyroxine (TSH < 0.1 mIU/L). Suppression of TSH may decrease the risk for recurrence and disease-specific mortality. The tailoring of TSH target range according to the extent of disease is important as maintenance of subclinical hyperthyroidism is also dangerous, since it increases the cardiovascular mortality. During long-term follow-up, the target TSH ranges should be adjusted to the response to therapy.

Which tumor marker can be used to follow up patients with DTC? How reliable is it?

The most important tumor marker of DTC during follow-up to estimate the therapeutic response and to detect the relapse of the disease is thyroglobulin (Tg). The currently used second-generation Tg assays have good diagnostic accuracy. Previous methods had lower sensitivity, and stimulated Tg was routinely used to increase the sensitivity. Stimulation should be done by levothyroxine withdrawal or by rhTSH. Tg values correlate with the tumor mass, and the stimulated value is about ten times higher than the basal (on-thyroxine) level. The major limitation of Tg is the presence of autoantibodies against it (TgAbs, thyroglobulin antibodies). TgAbs are found in 20–25% of DTC patients. TgAbs interfere with the measurement of Tg making it impossible to use as a primary tumor marker during follow-up.

Can thyroglobulin be used for the diagnosis of differentiated thyroid cancer?

Tg is a thyroid specific protein involved in thyroid hormone storage, but it is not specific for cancer as injury to the thyroid or inflammation (thyroiditis) can lead to thyroglobulin release as well. Tg is therefore not suitable for screening or initial diagnosis of DTC, and it is not included either in the diagnostic workup of thyroid nodules. On the other hand, Tg can be well exploited for the follow-up of differentiated thyroid cancer (see previous paragraph).

How DTC patients with TgAb positivity can be managed?

Persisting or rising TgAb levels may indicate the persistence or recurrence of the disease. However, compared to thyroglobulin values, their role in the detection of disease burden is not so definitive. TgAb titers reflect not only the thyroid cell (and tumor cell) volume but the immune reactivity against Tg. RAI treatment itself can

induce temporary elevation of TgAbs. However, in the long run, RAI treatment eliminates the remnant thyroid tissue as the autoantigen and contributes to the disappearance of TgAbs. The clearance of TgAbs in patients without residual disease needs approximately 2–3 years. The patterns of changes in the autoantibodies were influenced by the size of the tumor and by the age (longer time was required in younger patients) but could be just partially explained by known factors. However, it is generally accepted that patients who became antibody negative or show a significant decline in TgAb titers have lower recurrence rate compared to subjects with persisting or rising TgAbs. This is the reason why the 2015 ATA guidelines regarded the response to therapy in cases of rising TgAbs as "biochemical incomplete."

What kind of imaging can be used to evaluate the extent of disease in DTC patients?

The imaging methods are rather complimentary and all have advantages and disadvantages. The extent of diagnostic attempts to localize the residual or relapsing disease is not well defined. Neck US is the method of choice during follow-up for the evaluation of response to therapy 6–12 months after surgery (with or without RAI); it should be carried out by an experienced investigator. If local recurrence or pathological lymph nodes larger than 8–10 mm are detected, FNAB should be done. Diagnostic whole-body scan (DxWBS) should be performed to detect RAI avid metastases, but its sensitivity is low. The sensitivity of RAI scan can be increased by SPECT-CT or by applying larger, therapeutic doses (i.e., post-therapeutic scintigraphy). The diagnostic performance of ^{18}F-FDG PET-CT was more extensively investigated in TgAb-positive patients. A recent review and meta-analysis evaluating 9 studies (515 patients) found that ^{18}F-FDG PET or PET-CT demonstrated a moderate sensitivity (84%) and specificity (78%) for the detection of recurrent and/or metastatic diseases in DTC patients with progressively and/or persistently elevated TgAb levels and negative radioiodine WBS. Limitations of PET-CT are that the size of tumor foci may be under the detection limit of the method and well-differentiated cancer cells are not necessarily FDG-positive. Neck CT with contrast material is indicated in case of tracheal infiltration. Chest CT can detect mediastinal lymph node involvement or lung metastases. It is indicated if Tg is increasing and the neck US is negative. Neck MRI may have advantage in case of small cystic lymph node metastases.

What is the risk for recurrence in the presented case?

The prognosis of differentiated thyroid cancer is worse in older age, especially over 60 years. The age has been a risk factor in this case for poor outcome, but otherwise she had a small tumor with minimal extrathyroidal extension (ETE) and no lymph node metastases. The minimal ETE previously classified the patient to ATA intermediate risk for recurrence (Table 18.2) and pT3 (in AJCC/TNM seventh edition). PT3 was evaluated as high risk according to the ETA 2006 classification (Table 18.3). The minimal ETE does not change the tumor stage in AJCC/TNM eighth edition, so this patient would be categorized in 2018 as pT1 and low risk for recurrence. The minimal ETE was not found to increase rates of either cause-specific mortality or tumor recurrence. The detailed discussion of incompleteness of risk classifications is beyond the scope of this work, but this case represents many of the current uncertainties.

How is the initial response to therapy evaluated?

Since no decrease in the TgAb levels was observed 2 years after the operation and first RAI treatment, her therapeutic response is indeterminate (Table 18.4), and she underwent another course of RAI

Table 18.2 American Thyroid Association's Risk for Recurrence Classification 2009

Low risk	Intermediate risk	High risk
No local or distant metastases	Microscopic invasion of tumor into the perithyroidal soft tissues	Macroscopic tumor invasion
All macroscopic tumor has been resected	Cervical lymph node metastases or ^{131}I uptake outside the thyroid bed	Incomplete tumor resection
There is no tumor invasion of locoregional tissues or structures	Tumor with aggressive histology or vascular invasion	Thyroglobulinemia out of proportion to what is seen on the post-treatment scan
The tumor does not have aggressive histology		Distant metastases
No ^{131}I uptake outside the thyroid bed on the first post-treatment RAI scan		

Table 18.3 European Thyroid Association's Risk for Recurrence Classification 2006

Very low risk	Low risk	High risk
Unifocal T1 (≤1 cm) N0M0 and no extension beyond the thyroid capsule	T1 (>1 cm) N0M0	Any T3
	T2N0M0	Any T4
	Multifocal T1N0M0	Any T, N1
		Any M1

therapy. No RAI accumulation could be seen on SPECT-CT, but an unidentifiable morphological abnormality was found in the cranium; to exclude RAI non-avid metastases, PET/CT was also performed with a negative result. So, no structural disease was detected by any available imaging methods, even 2 years after the operation.

How the cervical nodal disease be managed?

What is the expected success rate of surgery?

The resolution of detectable structural disease by surgery is >80%, but a complete biochemical response could be achieved only in 30–50% of patients.

What is the success rate of RAI?

The efficacy of RAI therapy depends on the radiosensitivity of the tumor and the radiation dose delivered to cancer cells. Young patients with small tumor burden, high RAI uptake, lack of FDG uptake, and classical histological type are better candidates for effective RAI treatment. In a recent study investigating 357 patients with cervical lymph node metastases of DTC, successful ablation by two doses of RAI was achieved in 80.4% of patients. In another study, complete remission was found only in 28% of patients with a mean cumulative dose of 7.9 GBq RAI. The efficacy of RAI therapy was higher in patients with small metastatic lymph nodes, younger age, and lower Tg levels, so younger patients with small tumor mass responded better.

What is the role of percutaneous ethanol sclerotherapy?

US-guided percutaneous ethanol sclerotherapy (PEI) is usually considered in

Table 18.4 Evaluation of response to therapy (after radioiodine treatment)

Excellent	Indeterminate	Biochemical incomplete	Structural incomplete
No clinical, biochemical, or structural evidence of disease (on levothyroxine Tg <0.2 ng/ml, stimulated Tg <1 ng/ml)	Nonspecific biochemical findings without structural evidence of disease (on levothyroxine Tg 0.2–1 ng/ml, stimulated Tg 1–10 ng/ml, TgAb positivity with stable or declining antibody titer)	Abnormal Tg (on levothyroxine Tg >1 ng/ml, stimulated Tg >10 ng/ml) or rising TgAb levels in the absence of localizable disease	Persistent or newly identified locoregional or distant metastases

patients who have severe comorbidities and high risk for surgical complications after repeated neck explorations or refuse surgery. This method was found to be an excellent alternative of surgery in patients with a limited number of cervical lymph node metastases from PTC. In a study evaluating 63 patients, 93% of metastatic lymph nodes responded to PEI treatment of which 84% were solved completely, without significant side effects. One to three treatment sessions were required. The PEI was effective in our case; the metastatic lymph node decreased in size, and vascularization was not detected anymore.

What is the definition of RAI-refractory disease?

Few months later, multiple macronodular pulmonary metastases and a large mediastinal mass were discovered. Moderate level of RAI accumulation in the mediastinal mass was found on SPECT-CT after the third RAI treatment. However, an intensive FDG accumulation was observed in the pulmonary metastases. It was thus evaluated as RAI-refractory disease (Table 18.5).

Table 18.5 Definition of RAI-refractory disease

1. The malignant tissue did not ever concentrate RAI
2. The tumor was RAI-avid previously but lost the ability to concentrate RAI
3. RAI is concentrated in some lesions but not in others
4. Metastatic disease progresses despite significant concentration of RAI

What are the treatment options in RAI-refractory DTC?

The treatment of RAI-refractory disease depends on the rate of progression. In the lack of a sensitive tumor marker, the assessment of progression is difficult in TgAb-positive patients; only the size of metastases can be used for this purpose. In TgAb-negative patients, the rise of Tg or the short doubling time of Tg precedes the measurable growth of metastases. The presence of pulmonary metastases was unexpected after two negative WBS and a previously negative PET-CT. The appearance of macronodular pulmonary metastases was evaluated as progression of the disease; so a tyrosine kinase inhibitor (TKI) therapy was initiated. The patient did not tolerate the side effects, and it became evident during the next 3 years that there is only slow progression. Asymptomatic patients with RAI-refractory metastatic DTC who are stable or minimally progressive should be followed without additional therapy beyond TSH suppression. The

progression is determined according to the RECIST criteria: >20% increase of longest diameters of target lesions, development of new metastases, or disease-related symptoms may indicate systemic therapies.

What are the factors influencing the prognosis of patients with distant metastases?

Several studies investigated the prognostic factors for survival in patients with distant metastases of DTC. It is well-known that extrapulmonary distant metastases, the size of tumor foci, and RAI non-avidity are predictors of poor outcome. High FDG uptake is associated with less RAI uptake and vice versa. The median follow-up and progression-free survival (PFS) times in patients with lung-only distant metastases were 9.4 and 6.1 years, respectively. The 10-year PFS rate was 61.1%. Patients with macronodular pulmonary metastases had a significantly worse outcome, but even in this group, the 10-year PFS rate was 21% (versus 72% in patients with micronodular disease).

What can we expect from multitargeted kinase inhibitor therapy?

If progression of distant metastases has been established, systemic therapy is indicated. Multitargeted kinase inhibitors including sorafenib and lenvatinib have been shown to improve PFS; however, they have a special side-effect profile which can be difficult to tolerate for some patients. Sorafenib resulted in 41% improvement of PFS in the phase III DECISION trial. The SELECT trial investigating the efficacy of lenvatinib obtained 18.3 months of PFS compared to 3.6 months on placebo arm. The majority of side effects are common to different TKIs, such as hand-foot skin reaction, diarrhea, hypertension, and anorexia. The adverse events are usually mild to moderate and improve after dose reduction. The poor tolerability of these TKIs in the approved starting dose is reflected by the fact that approximately 65% of patients required at least one dose reduction in both clinical trials. Considering the long PFS of DTC patient with distant metastases, the proper timing of a TKI treatment has a critical importance. The major clinical trials included patients with radiologically proved progression in the last 12–14 months. Rapid increase in size of metastases (>10 mm), symptomatic metastases, large tumor mass, high Tg level, and short Tg doubling time are indications for TKI treatment. Based on phase III trials, the type of driver mutations (BRAF or RAS) is not predictive for outcome. The cessation of therapy is also questionable. The oncologic treatment should be stopped in case of progression; the abrupt withdrawal of the inhibitors of proliferation pathways may result in a more rapid growth of the tumor.

Tips

The chapter "Thyroid Nodule and Multinodular Goiter" is suggested to be read for a detailed discussion of preoperative diagnosis of DTC (▶ Chap. 15). Medullary thyroid cancer is discussed in the next chapter (▶ Chap. 19).

Take-Home Messages

- Differentiated thyroid cancer (DTC) generally has an excellent prognosis, but locoregional or distant metastasis may develop many years after the first treatment.
- Lifelong follow-up investigations are required in this disorder.
- In cases of thyroglobulin antibody (TgAb) positivity, thyroglobulin cannot be used as a tumor marker during follow-up, and the change in the TgAb titer provides similar but not so accurate information about the residual disease.
- The neck US is part of the routine diagnostic workup; residual disease should be looked for by other imaging methods

(WBS, SPECT-CT, PET-CT) in case of rising TgAb titer.
- The estimation of risk for recurrence carries uncertainty.
- Cervical nodal disease can be solved by surgery, radioiodine (RAI) treatment, or percutaneous ethanol sclerotherapy.
- Distant metastases develop in 7–10% of DTC cases, and two-thirds of these patients become RAI-refractory.
- The treatment of RAI-refractory disease depends on the rate of progression.
- Multitargeted kinase inhibitors including sorafenib and lenvatinib have been shown to improve progression-free survival.

Acknowledgment This work was supported by a Human Resources Development Operational Programme Grant (EFOP-3.6.1-16-2016-00004) and a Higher Education Institutional Excellence Programme Grant of the Ministry for Innovation and Technology in Hungary within the framework of the second thematic program of the University of Pécs.

Thanks to Erzsebet Schmidt for providing images to Fig. 18.2.

Suggested Reading

1. Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, de la Fouchardiere C, Pacini F, Paschke R, Shong YK, Sherman SI, Smit JWA, Chung J, Kappeler C, Pena C, Molnar I, Schlumberger MJ, Investigators D. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet. 2014;384:319–28. https://doi.org/10.1016/s0140-6736(14)60421-9.
2. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM, ATA. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19:1167–214. https://doi.org/10.1089/thy.2009.0110.
3. Gild ML, Topliss DJ, Learoyd D, Parnis F, Tie J, Hughes B, Walsh JP, McLeod DSA, Clifton-Bligh RJ, Robinson BG. Clinical guidance for radioiodine refractory differentiated thyroid cancer. Clin Endocrinol. 2018;88:529–37. https://doi.org/10.1111/cen.13508.
4. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American Thyroid Association management guidelines for adult patients with Thyroid nodules and differentiated thyroid cancer the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid. 2016;26:1–133. https://doi.org/10.1089/thy.2015.0020.
5. Jeong SY, Baek JH, Choi YJ, Lee JH. Ethanol and thermal ablation for malignant thyroid tumours. Int J Hyperth. 2017;33:938–45. https://doi.org/10.1080/02656736.2017.1361048.
6. Lamartina L, Borget I, Mirghani H, Al Ghuzlan A, Berdelou A, Bidault F, Deandreis D, Baudin E, Travagli JP, Schlumberger M, Hartl DM, Leboulleux S. Surgery for neck recurrence of differentiated thyroid cancer: outcomes and risk factors. J Clin Endocrinol Metabol. 2017;102:1020–31. https://doi.org/10.1210/jc.2016-3284.
7. Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JWA, Wiersinga W, Moreno-Reyes R, Van den Bruel A, Zira C, Feldt-Rasmussen U, Godballe C, Corone C, Borson-Charzot F, Reiners C, Alevizaki M, Duntas L, Vlassopoulou B, Esik O, Mezosi E, Moriarty MJ, Smyth P, Cohen O, Krausz Y, Pellegriti G, Castagna MG, Marga M, Bioro T, Jarzab B, Carrilho F, de Castro JJ, Limbert ES, Ioachim D, Mogos V, Ursu H, Roumiantsev P, Troshina E, Hnilica P, Besic N, Zagar I, Gomez JM, Sanchez-Franco F, Berg G, Tennvall J, Wallin GK, Meier CA, Links TP, Ayvaz G, Uysal AR, Cherenko S, Larin O, Harmer C, European Thyroid Canc T. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol. 2006;154:787–803. https://doi.org/10.1530/eje.1.02158.
8. Ringel MD, Nabhan F. Approach to follow-up of the patient with differentiated thyroid cancer and positive anti-thyroglobulin antibodies. J Clin Endocrinol Metabol. 2013;98:3104–10. https://doi.org/10.1210/jc.2013-1412.
9. Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, Habra MA, Newbold K, Shah MH, Hoff AO, Gianoukakis AG, Kiyota N, Taylor MH, Kim SB, Krzyzanowska MK, Dutcus CE, de las Heras B, Zhu JM, Sherman SI. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med. 2015;372:621–30. https://doi.org/10.1056/NEJMoa1406470.
10. Tuttle RM, Haugen B, Perrier ND. Updated American Joint Committee on cancer/tumor-node-metastasis staging system for differentiated and anaplastic thyroid cancer (eighth edition): what changed and why? Thyroid. 2017;27:751–6. https://doi.org/10.1089/thy.2017.0102.

Medullary Thyroid Cancer

Géza Nagy

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_19

Opening

In this chapter while following the clinical course of a patient diagnosed with medullary thyroid cancer (MTC), the reader will be acquainted with the basic clinical features, diagnosis, and treatment of this rare tumor.

Definition of the Disease

Medullary thyroid cancer (MTC) is a rare malignant tumor, accounting for about 3–5% of all thyroid carcinomas. The tumor cells are of neuroendocrine origin, arising from the calcitonin-secreting parafollicular C-cells. The majority of MTC cases are sporadic with no known environmental risk factors, however as much as a quarter of the cases may be genetically determined and caused by germ-line-activating mutations in the rearranged during transfection (*RET*) proto-oncogene in the context of the multiple endocrine neoplasia type 2 syndrome (MEN2). Beside differentiated thyroid cancer (papillary and thyroid cancer) and MTC, the fourth form of thyroid cancer is termed anaplastic thyroid cancer that has the worst prognosis with rapid progression z

Case Presentation

A 57-year-old male patient with no previous medical history was referred to our Endocrine Department with complaints including change of stool habit and chronic diarrhea. Prior to his requested endocrine evaluation, the patient was evaluated in detail for gastroenterological causes of his complaints, yet no cause of his symptoms could be found.

After his admission, a palpable, non-tender mass was found in the enlarged right lobe of the thyroid gland as well as 1–2 cm large and stony-hard, non-tender lymph nodes on both sides in the cervical regions. There were no signs of exophthalmos, hyperpigmentation, flushes, or facial plethora. His blood pressure and pulse was normal, and there were no further significant abnormal findings on a thorough physical examination.

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What endocrine disorders should be considered in the differential diagnostics of chronic diarrhea?

The most frequent endocrine disorders that may be associated with these gastrointestinal (GI) complaints, such as hyperthyroidism, hypoparathyroidism and complications of diabetes mellitus can be easily evaluated by routine assessment of thyroid stimulating hormone (TSH), glycated hemoglobin (HbA1c), blood glucose, and serum calcium levels. In rare cases of chronic diarrhea, when the clinical picture raises the suspicion, primary adrenal insufficiency, gastrinoma (Zollinger-Ellison's syndrome) or carcinoid syndrome might be investigated. Even more infrequently, other duodenopancreatic neuroendocrine tumors such as vasoactive intestinal peptide (VIP) producing VIP-oma and glucagonoma might also be associated with chronic diarrhea. Carcinoid syndrome and gastrinoma are discussed in detail in the Part on neuroendocrine tumors and paraneoplastic endocrine syndromes (► Chaps. 44 and 48). ► Box 19.1 summarizes the major endocrine causes of chronic diarrhea.

What kind of other symptoms may be associated with MTC?

Some patients present flushing, and if the tumor secretes adrenocorticotropic hormone (ACTH), very rarely, ectopic ACTH syndrome can be observed (► Chap. 45).

Box 19.1 Endocrine Causes of Chronic Diarrhea

Common and rare endocrine causes of chronic diarrhea

- Hyperthyroidism
- Diabetes mellitus
- Hypoparathyroidism
- Addison's disease
- Hormone-secreting neuroendocrine tumors
  - Carcinoid syndrome
  - Gastrinoma
  - VIP-oma
  - Glucagonoma
  - Medullary thyroid cancer

Are there alterations in MTC with regard to calcium-related parameters?

Despite being relevant in the regulation of calcium homeostasis in non-mammal vertebrates, calcitonin does not have a major role in regulating calcium homeostasis in humans. Even significant overproduction of calcitonin cannot be clearly associated with serum calcium alterations. On the other hand, total thyroidectomy, and therefore the loss of calcitonin-producing C-cells, does not affect calcium homeostasis either, provided that the parathyroid glands are left intact. On the other hand, calcitonin can be used in pharmacological doses for the treatment of severe hypercalcemia, but its effect is transient.

Case Presentation Continued

Even though in the presented case, TSH level was normal (1.122 mIU/L) ruling out hyperthyroidism, the clinical picture clearly pointed to a thyroid pathology.

What tests should be done to investigate the palpable structural abnormalities found in the thyroid gland and the surrounding cervical regions in this patient?

The best first choice of thyroid imaging is ultrasonography (US). It has a high sensitivity and is specific enough to discover lesions suspected to be pathological or malignant (see in detail ▶ Chap. 15 on Thyroid nodule and multinodular goiter). In case of suspicion, US-guided fine-needle aspiration (FNA) is a quick and easy way to gain samples for cytological examination.

The thyroid US in our patient showed a single solid hypoechogenic nodule in the right lobe with punctate echogenic foci, and extra-thyroidal extension. The US features of the nodule defined by the Thyroid Imaging, Reporting and Data System (TIRADS) indicated a score of 11 implying that the nodule is highly suspicious for malignancy. The left lobe showed no signs of abnormality. The examination also revealed multiple bilateral lymphadenopathy with pathological lymph nodes ranging from 15 to 40 mm is diameter (see ◘ Fig. 19.1).

FNA was performed on the thyroid nodule. The cytological smear showed isolated, round, large polygonal cells presenting signs of malignancy resembling MTC. Immunohistochemistry was positive for chromogranin A and thyroid transcription factor-1 (TTF1). Later as part of a palliative surgical approach, the histological examination of a metastatic lymph nodule has also been performed, and the microscopic images confirming MTC are presented from this specimen in ◘ Fig. 19.2.

Are there tumor markers for MTC?

Calcitonin, the product of C-cells, and carcinoembryonic antigen (CEA) can be exploited as tumor markers in MTC. In contrast with other tumors, where tumor markers can only be exploited for the monitoring of tumor progression (e.g., CEA for colorectal cancer), calcitonin can be used in the diagnosis of MTC, as well,

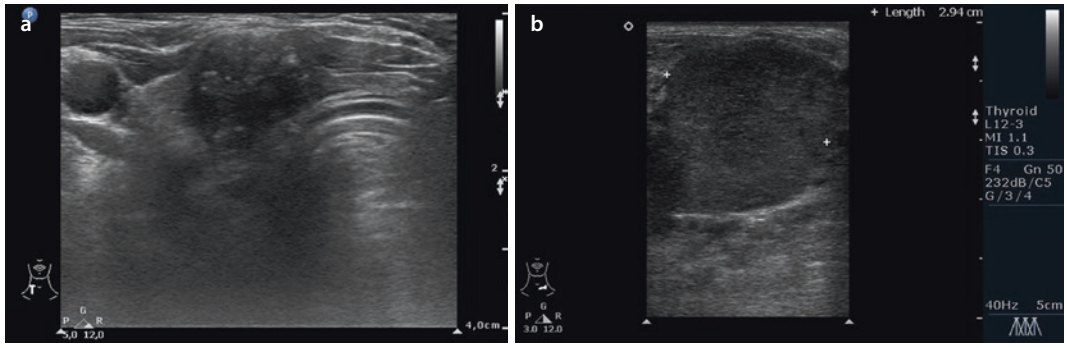


Fig. 19.1 Ultrasonographic images of a right sided MTC **a** and a pathological hypoechoic lymph node on the left side **b**

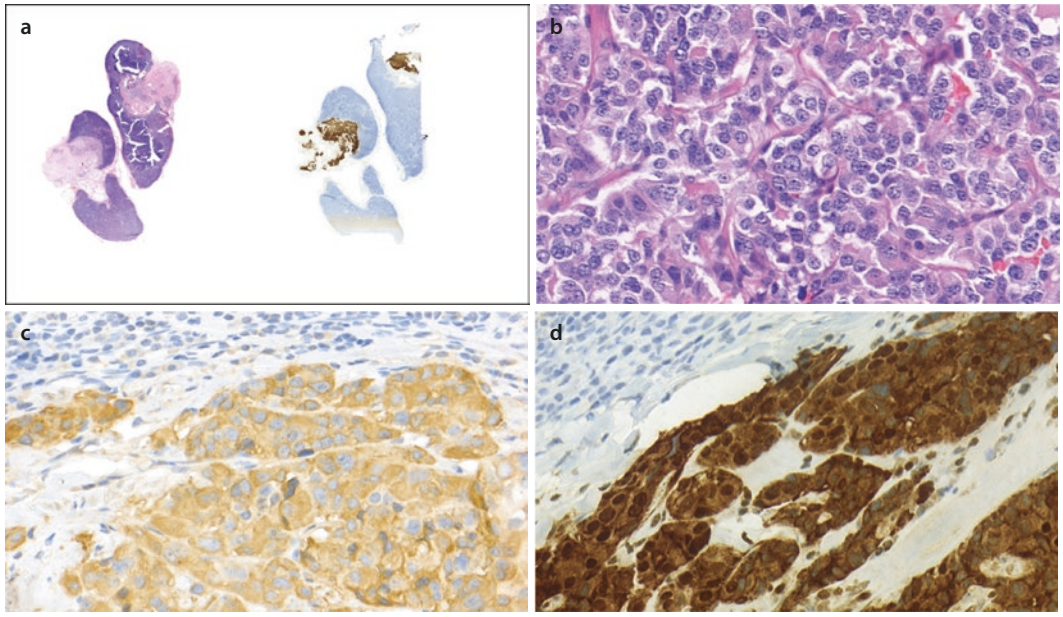


Fig. 19.2 Lymph node metastasis of MTC. **a** Hematoxylin-eosin staining and CEA immunohistochemistry presenting extranodular spread of the tumor. **b** Hematoxylin-eosin staining. **c** Calcitonin **d** CEA

but this issue is controversial (basal or stimulated calcitonin, questions of false positive calcitonin etc. – see later) and calcitonin is not universally used as a tumor marker in the evaluation of suspicious thyroid nodules.

In our patient, serum calcitonin (6250 pg/mL; normal range 0–19) and CEA (1510.0 ng/mL, normal range: 0.0–4.3) levels were highly elevated. After the diagnosis was confirmed, the patient was tested for germline *RET* mutations. The test confirmed that in this case the MTC had no genetic background and should be regarded as a sporadic neoplasm.

In case of uncertain cytological and tumor marker results what additional tests could be used to demonstrate that the tumor is MTC?

In early stage MTC serum calcitonin concentration may only be mildly elevated

(under 100 pg/mL), and also the cytological diagnosis may be indeterminate. Under these circumstances, causes that may false positively elevate calcitonin levels in the blood (listed in ◘ Table 19.1) should be ruled out. In certain centers, pentagastrin (0.5 μg/kg) or calcium (2.5 mg Ca/kg)-stimulated calcitonin is used to enhance the accuracy of MTC diagnosis. These tests are non-invasive, easy to do, and a 5×–10× elevation of stimulated calcitonin levels within minutes (usually above 200 pg/mL) indicates MTC, whereas in other non-MTC causes, the calcitonin increase is limited or absent.

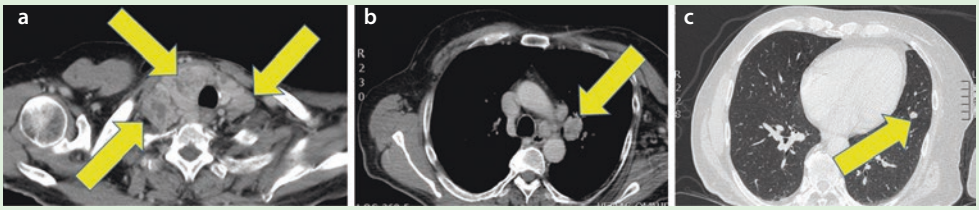
If false positively elevated calcitonin could be ruled out, an US-guided fine-needle aspiration from the suspected nodule or a metastatic lymph node along with high calcitonin measured in the needle washout fluid is an indicator of MTC.

◘ **Table 19.1** Non-MTC-related causes of elevated calcitonin and CEA levels

Calcitonin	CEA
Hypercalcemia	Gastrointestinal tract inflammatory disease
Hypergastrinemia	Benign lung disease
Neuroendocrine tumors	Non-thyroid malignancies (i.e., colorectal cancer)
Renal insufficiency	Cigarette smoking
Papillary and follicular thyroid carcinomas	Heterophilic antibodies
Goiter	
Chronic autoimmune thyroiditis	
Heterophilic antibodies to calcitonin	
Drugs: proton pump inhibitors, beta blockers, glucocorticoids	

Case Presentation Continued

After the establishment of the diagnosis of MTC, further testing was necessary to determine the stage of the disease. Highly elevated tumor markers suggested the presence of distant metastases, which was confirmed by cross-sectional imaging. Besides the known MTC in the right lobe of the thyroid gland invading the surrounding soft tissue, and gross bilateral lymphadenopathy in the cervical lesions, distant metastases in the mediastinum, pulmonary hila and multiple pulmonary metastases in both lungs of about 1 cm were found (see ◘ Fig. 19.3). One suspected bone metastasis was identified in the manubrium of the sternum.



◘ **Fig. 19.3** Contrast-enhanced CT images in venous phase of neck **a** and thorax **b**, **c**) demonstrating locally invasive MTC with cervical and hilar lymph node metastasis and lung metastasis (yellow arrows)

Are the patient's GI symptoms caused by MTC?

Probably yes. Diarrhea is a common complaint in patients with advanced metastatic MTC. The exact cause in not well understood, however calcitonin-induced GI hypermobility and hypersecretion might play a role. The symptoms may be severe, causing poor life quality and even cachexia due to malabsorption. Besides lifestyle modifications such as low fiber diet, and avoiding alcohol intake, usually medical treatment is needed. First-line treatment options include anti-motility agents such as loperamide. In more severe cases, tumor debulking or chemoembolization of gross distant metastases may help alleviate the symptoms.

Is routine genetic testing necessary in this patient with MTC?

Yes. Since 25% MTC patients carry germline mutation in the *RET* gene causing MEN2 syndrome, when the diagnosis of MTC has been established, genetic analysis should always be performed. This allows detection or even prevention of hereditary endocrine tumors in the index patient (prophylactic thyroidectomy), and first degree relatives, as well. In case of a positive *RET* mutation, screening for pheochromocytoma and primary hyperparathyroidism are warranted (see in ▶ Chap. 51 on Multiple Endocrine Neoplasia type 2).

Are there any curative treatment options in this patient's case?

Unfortunately, there aren't any. The only curative method in MTC is total surgical resection of the tumor. Most commonly total thyroidectomy and central and lateral compartment lymph node dissection is recommended based on the cervical extent of the disease. The surgical plan is usually based on imaging (US and CT) and serum calcitonin concentrations. Calcitonin levels less than 20 pg/ml almost rule out the possibility of lymph node metastases. The higher the calcitonin value, the more advanced the disease might be spreading. Thus in case of calcitonin values between 20 and 500 pg/ml, the presence of metastases should always be checked in the ipsi- and contralateral central and lateral neck regions in order to be prepared for total surgical resection. Common side effects of an extended surgery includes hypoparathyroidism, thus patients must be monitored for hypocalcemia. The success of the operation can be determined 3 months postoperatively by reassessing tumor markers and performing imaging.

In this case, however, both serum calcitonin (6250 pg/mL) and imaging studies indicated the systematic spread of the disease thus curative resection was not an option.

What is the prognosis of the patient presented?

The clinical course of sporadic MTC is unpredictable. Some patients may have long progression-free disease course; however, in some cases the progression is rather fast. The most important prognostic factors include age and stage of the disease at the time of diagnosis. Unfortunately this patient had cervical and distant metastases at the time the diagnosis was made, meaning that he was in Stage IVC, indicating 100% mortality caused by MTC and a less than 21% 10-year survival (see ◘ Table 19.2).

Are there any other prognostic factors in MTC? How could the progression of MTC be followed?

Follow-up of the tumor burden with sequential imaging is one way of evaluating disease progression. This can be complemented by controlling serum tumor markers over multiple time points (i.e., every 3 months) to assess the time at which the values of these markers value double.

Table 19.2 Overall survival and mortality rates in MTC based on Tumor Node Metastasis (TNM) stage

TNM		10-year survival	Mortality due to MTC
Stage I	T1, N0, M0	100%	0%
Stage II	T2, N0, M0	93%	13%
	T3, N0, M0		
Stage III	T1,N1a,M0	71%	56%
	T2,N1a,M0		
	T3,N1a,M0		
Stage IV A	T4a,N0,M0	21%	100%
	T4aN1a,M0		
	T1,N1b,M0		
	T2,N1b,M0		
	T3,N1b,M0		
	T4aN1b,M0		
Stage IV B	T4b, any N, M0		
Stage IV C	Any T, any N, M1		

Doubling times (DTs) of serum calcitonin and CEA values have been shown to predict aggressiveness and the rate of disease progression as well as overall survival in metastatic MTC. The less time elapses between the doubling of tumor markers, the more aggressive tumor is. For example, in case of a DT of less than 6 months is associated with a 10-year survival of 8%, whereas in DT-s between 6 and 24 months and above, 10-year survival rate increases to 37% and 100% respectively.

When is palliative intervention indicated in MTC?

Metastatic MTC is commonly resistant to palliative medical, radio-, or surgical therapy. Side effects of medical treatment and complications of more invasive treatment options are commonly significant. On the other hand, some patients may have slow tumor progression with a good quality of life for years. Thus palliative interventions are recommended only in patients who show signs of rapidly progressive disease or uncontrollable hormonal activity. In case of space-occupying, painful tumor mass causing breathing or swallowing difficulties by compression of the spinal cord, trachea, and the esophagus, palliative surgery or external beam radiation therapy (EBRT) may be indicated. Also, symptoms of hormone activity of the tumor resistant to first-line treatment options may indicate of palliative therapy such as chemoembolization of liver metastases.

Is TSH suppression indicated in MTC?

No, since the MTC is not a differentiated thyroid neoplasm and C-cells do not express the TSH receptors, there is no reason to suppress TSH below the normal range. However, thyroid hormone replacement is usually needed after total thyroidectomy to maintain euthyroidsm.

Case Presentation Continued

In the presented case, after diagnosis was made, the patient's diarrhea was well controlled using anti-motility agents. His disease was stable. He was in good condition and was able to work, thus there were no indications for palliative interventions. The patient was observed with tumor markers and CT imaging and bone scintigraphy for 2 years with no signs of significant tumor growth. However, in the third year of observation, calcitonin DT decreased to 1.03 years, and growth in primary and metastatic tumor size, and new bone and intraabdominal lymph node metastases were detected indicating significant disease progression. The majority of the tumor burden was localized in the cervical region, causing limited neck and

head movement. Interestingly, the patient never developed liver metastases which are otherwise common in MTC.

In order to stop disease progression 300 mg vandetanib was chosen as first-line systemic therapy. To prevent pathological fractures due to metastases in the hip and lumbar vertebrae, iv. bisphosphonates were also administered. Vandetanib is a multi-kinase inhibitor, that acts on *RET*, EGFR (epidermal growth factor receptor) and VEGFR (vascular endothelial growth factor receptor) kinases expressed on MTC cells and has shown efficacy in symptomatic or progressive locally advanced or metastatic MTC. Even though adverse events such as diarrhea, fatigue, rash and folliculitis, photosensitization, hypertension, and prolongation of the QT interval are quite frequent during vandetanib treatment, we have observed none. Changes of tumor markers during the 10 months of treatment period are presented in Fig. 19.4. Vandetanib was eventually discontinued due to tumor advancement. After failure of this first-line therapy, patient was switched to second-line 140 mg/day cabozantinib (another tyrosine kinase inhibitor targeting *RET*, VEGFR, and hepatocyte growth factor (HGF) receptor), which he tolerated well. After 3 months of treatment, stable disease has been indicated by imaging, and a significant decrease in serum calcitonin levels has been observed (presented in Fig. 19.4). Unfortunately, 6 months after beginning cabozantinib treatment, further progression was seen, and the patient developed new cutaneous metastases, and had some difficulty swallowing. As a last resource, dacarbazin and 5-Fluorouracil based systemic chemotherapy has been started and palliative surgical intervention was planned, as well. Unfortunately, and somewhat unexpectedly on the morning of the planned interventions, the patient was found dead 4 years and 5 months after the initial diagnosis. He deceased with no alarming signs and was seen in good condition few hours before. Since autopsy has not been performed as requested by the patient's family, the true reason of death could not be determined. The most possible cause of death could have been aspiration or cardiac arrest.

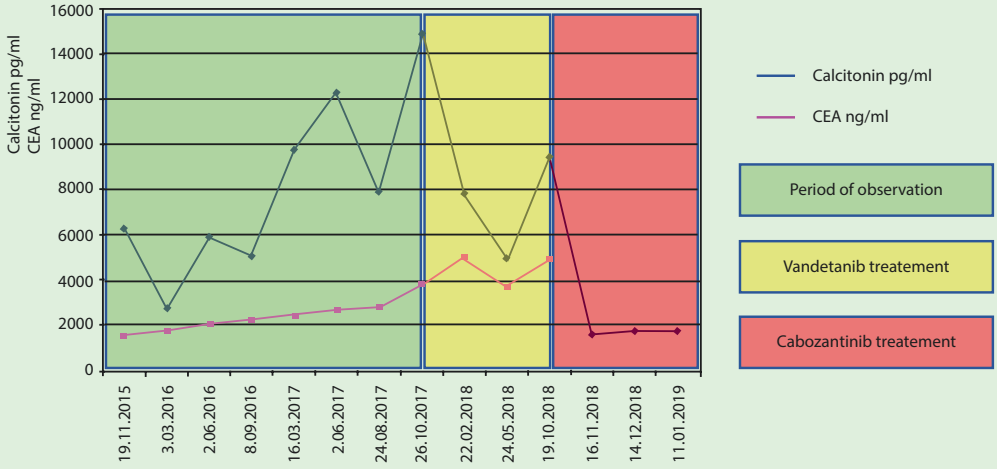


Fig. 19.4 Change of tumor markers during observational and treatment phases

Tips

The reader is advised to read (or repeat) the chapters on thyroid nodule and multinodular goiter (▶ Chap. 15) and differentiated thyroid cancer (▶ Chap. 18) for better understanding of nodular thyroid disease as a whole. Moreover, the chapter on Multiple Endocrine Neoplasia type 2 (▶ Chap. 51) is worth reading as 25% of MTC patients might be affected by MEN2.

Take Home Messages

- Medullary thyroid cancer (MTC) is a rare malignant tumor of the thyroid gland, usually discovered at an advanced stage and has a poor prognosis.
- Most cases of MTC-s are sporadic, however 25% are caused by mutations of the *RET* gene and show an autosomal dominant inheritance.
- In inherited MTC, pheochromocytoma and primary hyperparathyroidism should be screened at and after the diagnosis regularly.
- Calcitonin and CEA are specific tumor markers of MTC that have relevance in estimating tumor burden and also have prognostic value.
- Traditional chemotherapy is usually not effective in treating MTC.
- Tyrosine kinase inhibitors (TKIs) are palliative therapeutic options with several side effects and are currently available with limited eficacy.

Suggested Reading

1. Adam MA, Thomas S, Roman SA, Hyslop T, Sosa JA. Rethinking the current American Joint Committee on cancer TNM staging system for medullary thyroid cancer. JAMA Surg. 2017;152(9):869–76. https://doi.org/10.1001/jamasurg.2017.1665.
2. Barbet J, Campion L, Kraeber-Bodere F, Chatal JF, Group, G. T. E. S. Prognostic impact of serum calcitonin and carcinoembryonic antigen doubling-times in patients with medullary thyroid carcinoma. J Clin Endocrinol Metab. 2005;90(11):6077–84. https://doi.org/10.1210/jc.2005-0044.
3. Grant EG, Tessler FN, Hoang JK, Langer JE, Beland MD, Berland LL, Teefey SA. Thyroid ultrasound reporting lexicon: white paper of the ACR Thyroid Imaging, Reporting and Data System (TIRADS) Committee. J Am Coll Radiol. 2015;12(12 Pt A):1272–9. https://doi.org/10.1016/j.jacr.2015.07.011.
4. Tsang VHM. Management of treatment-related toxicities in advanced medullary thyroid. cancer. Curr Opin Oncol. 2019;31(3):236–42. https://doi.org/10.1097/CCO.0000000000000534.
5. Viola D, Elisei R. Management of Medullary Thyroid Cancer. Endocrinol Metab Clin North Am. 2019;48(1):285–301. https://doi.org/10.1016/j.ecl.2018.11.006.
6. Wells SA Jr, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, American Thyroid Association Guidelines Task Force on Medullary Thyroid, C. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid. 2015;25(6):567–610. https://doi.org/10.1089/thy.2014.0335.

Thyroid Hormone Resistance

Luca Persani and Irene Campi

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_20

Opening

In this chapter, the reader will get familiar with the clinical features and treatment of resistance to thyroid hormone syndrome. The differential diagnosis of Thyroid-stimulating hormone (TSH)-secreting pituitary adenoma is also discussed here.

Definition of the Disease

Thyroid hormone resistance to (RTH) is a genetic syndrome characterized by impaired peripheral sensitivity to thyroid hormone (TH).

The first family affected with RTH, described by Refetoff and collaborators had elevated levels of T4 and T3 with unsuppressed serum TSH levels, deaf-mutism and skeletal abnormalities as a consequence of a large homozygous deletion of the THRB gene, encoding for the TH receptor beta (TRβ). Later, patients harboring heterozygous dominant-negative mutations in the THRB have been identified.

During the last two decades, the definition of RTH expanded with the identifications of an increasing number of syndromes of reduced responsiveness to TH. Defects in the TH transporter monocarboxylate transporter 8 (MCT8) cause the Allan–Herndon–Dudley syndrome characterized by severe neurological phenotypes and high Free triiodothyronine (FT3) levels. Genetic mutations in the selenocysteine insertion sequence-binding protein 2 (SECISBP2) cause a loss of function of the deiodinases. The consequence is an abnormal metabolism of TH, characterized by high levels of FT4, low-normal FT3, and a slightly increased TSH. Finally, in 2012, mutations in the TH receptor alpha (TRα) have been discovered. This latter was named RTHα, while the original syndrome described by Refetoff was renamed as RTHβ.

In RTHβ, the insensitivity of the pituitary to TH causes a compensatory increase of T4 and T3 to overcome the impaired function of a mutant TRβ. The consequence is a central, TSH-dependent hyperthyroidism.

The different tissue distribution of TR isoforms is responsible for the phenotype of RTHβ patients, who exhibit thyrotoxic features in organs where TRα predominates (central nervous system, skeletal muscle, myocardium, bone, and intestine), and manifestations of hypothyroidism in tissues expressing the TRβ (liver, cochlea, and retina).

RTHβ has an autosomal dominant inheritance and an estimated prevalence of 1:20,000–40,000.

This is probably underestimated, since most of the screening programs for congenital hypothyroidism are based on the sole TSH determination which is typically normal in RTHβ. Also, in adults the assessment of thyroid function tests is often performed by a reflex-TSH strategy, thus free THs are measured only when the TSH is abnormal.

Case Presentation

A 18-year-old man was referred to our Clinic for discrepant TH function tests (TFTs) found during preoperative investigations for a cardiac ablation (TSH 4.5 mIU/ml normal: 0.4–4.3; FT4: 45 pmol/l normal: 11.5–24.5, FT3 10.3 pmol/l normal: 2.9–7.1).

The patient's physical examination showed a small goiter, hyperhidrosis, and tremors in the upper limbs. His past history included panic disorder treated with paroxetine.

Two years earlier, he was found to have cardiomegaly and stress-induced tachycardia and was excluded from competitive sports. Lately, a 24-hour Holter monitoring showed an episode of supraventricular tachycardia (SVT) at 160 beats/min. He was scheduled for catheter

ablation which was not performed, following a normal electrophysiological study.

Anti-thyroid peroxydase (anti-TPO) antibodies were positive and the thyroid gland appeared enlarged (26 ml) and with a heterogeneous echotexture by ultrasound (US). Thyroid scan showed a diffusely increased pertechnetate uptake in both lobes. These features were misinterpreted as Graves' disease and methimazole was started. After 1 month, FT4 and FT3 normalized while the TSH rose to 26 mUI/L, and the treatment was discontinued.

What can be observed from this hormone panel and what kind of diseases should be considered?

The patient had elevated FT4 and FT3 levels with an inappropriately high TSH.

This inappropriate secretion of TSH is the hallmark of central (secondary) hyperthyroidism, a rare condition encompassing RTHβ and TSH-secreting pituitary adenomas (TSH-oma). TSH-oma is the rarest form of pituitary adenoma (annual incidence of 1–2/million).

It is noteworthy that assay interferences due to familial dysalbuminemic hyperthyroxinaemia, heterophilic antibodies, paraproteins, anti-T4/anti-T3 autoantibodies, and certain drugs cause a similar biochemical picture (Table 20.1 and Fig. 20.1).

Is it possible to differentiate the possible causes of central hyperthyroidism based on clinical symptoms?

The symptoms of RTHβ may be misleading and overlapping with those of TSH-oma patients. Although in the latter, the sensitivity to TH is conserved, the slow progression of the hyperthyroidism may explain the lack of severe manifestations.

There are some clues that might argue for RTHβ, particularly the presence of relatives with recurrence of central hyperthyroidism. In this case, the mother and the sister had normal TH function tests (TFTs), while the father was unavailable. Indeed, 85–90% of RTHβ cases are familiar, while dominant inheritance of a TSH-oma has been exceptionally described in two families with Multiple Endocrine Neoplasia 1 (MEN1, ▶ Chap. 51).

Also, the age of the patient may help the diagnosis, as TSH-omas are often diagnosed later, usually in the 5th to 6th decades of life and pediatric and juvenile cases are very rare.

Which tests can be used for the differential diagnosis of central hyperthyroidism? Are imaging techniques helpful?

The diagnostic flow-chart is presented in Fig. 20.1.

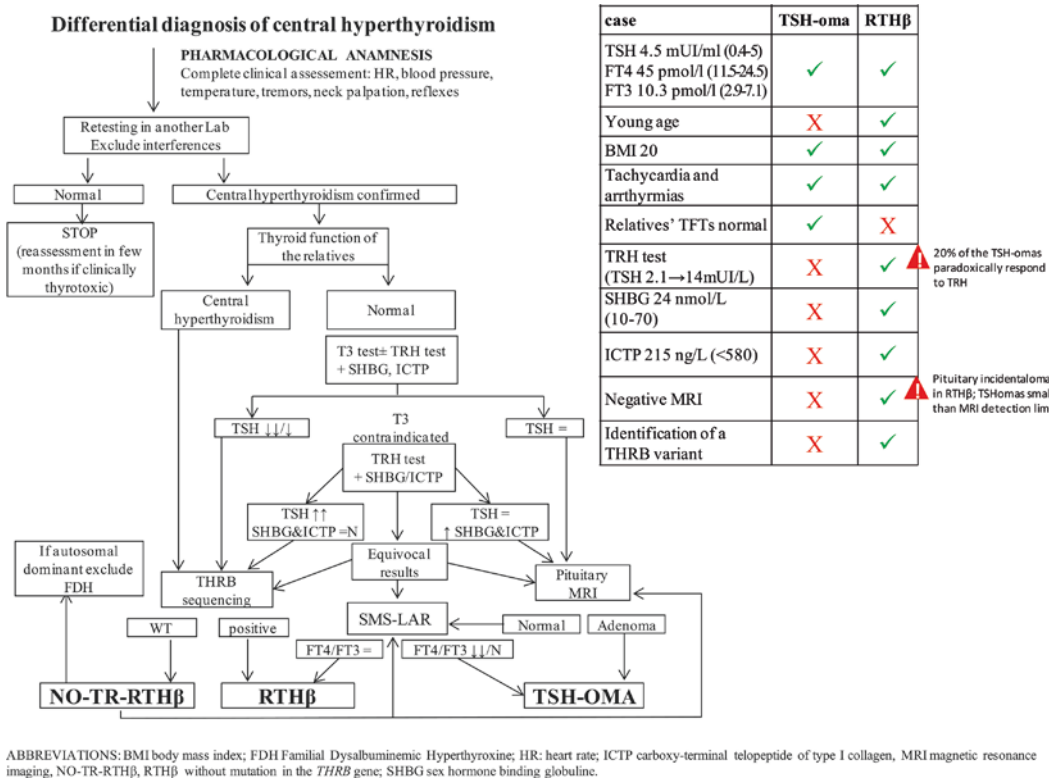
1. The first step is the *exclusion of assay interferences* in TFTs, an often overlooked source of mismanagement. Central hyperthyroidism was confirmed in both a one-step and a two-steps assay platform. TFTs should be rechecked in a different laboratory, as some methods are more prone to interferences than others. In this case, given the associated autoimmune thyroid disease (AITD) and the increased pertechnetate uptake, we also ruled out a possible overestimation of TSH levels due to heterophilic antibodies and macro-TSH, masking a primary hyperthyroidism. This eventuality was excluded by measuring the TSH after PEG (polyethylene glycol)-precipitation (recovery rate of 90%) and by the perfect linearity of a dilution experiment. Moreover, anti-TSH-receptor antibodies were negative. (Macro-TSH is a phenomenon similar to macroprolactinemia described in the chapter on Prolactinoma (▶ Chap. 1)).

Table 20.1 Differential diagnosis of RTHβ

Condition	Etiology	TFTs and markers of thyroid actions					Thyrotoxic features	Hypothyroid features	Pituitary sensitivity	Other characteristics/ associations
		TSH	FT4	FT3	r-T3	SHBG				
Defect of THRB gene (RTHβ)	Genetic (*THRB*); AD	N/ Slight↑	↑	↑	↑	N	Variable (heart/ bone)	Compensated (liver, retina, and hearing system)	Impaired	ADHD
Defect of THRA gene (RTH α)	Genetic (*THRA*); AD	N	Borderline/ slight↓	↑	↓	↑	Mild, (liver)	Variable (CNS, heart, intestine, and skeleton)	Normal	Variable cognitive deficits, anemia, dysmorphic face, macrocephaly, delayed growth, and constipation
Defect of TH transport (Allan-Herndon-Dudley syndrome)	Genetic *(MCT8)*; X-linked	N/ slight↑	Slight↓	↑	↓	↑	Severe (skeletal muscle, liver, and heart)	Severe (CNS)	Impaired	Severe mental retardation; muscle wasting, low body weight, scoliosis, and spastic quadriplegia
Defect of TH metabolism (SBP2 deficiency)	Genetic *(SBP2)*; AR	N/ slight↑	↑	N/slight↓	↑	N	–	Compensated; symptoms of multiple selenoprotein deficiencies	Normal	Insulin sensitivity, myopathy, azoospermia, anemia, and lymphopenia
Amiodarone treatment/iodine	Exposure to excessive iodine	N/ slight↑	↑	N/slight↓	↑	N	–	–	Normal	Pharmacological anamnesis drives diagnosis
Furosemide, salicylates, diclofenac, and naproxen	Transient T4/T3 displacement from TBG/ albumin	N/ slight↓	↑	↑	NA	NA	–	–	Normal (acute TSH↓)	
Heparin	T4 displacement by FFA (increased LPL activity)	N	↑	NA	NA	NA	–	–	Normal	

Familial Dysalbuminemic Hyperthyroxinemia (FDH)	Genetic (*ALB*); AD; increased TH binding to albumin (competitive assays)	N	N/ spuriously↑	N/ spuriously↑	N	N	–	–	Normal	Source of mismanagement if overlooked
HAMA, anti-T4/ anti-T3 autoAb	Sequestration of TH analogs (competitive assays)	N	N/ spuriously↑	N/ spuriously↑	N	N	–	–	Normal	
Macro-TSH, HAMA	Cross-link with Ab (sandwich assays)	↑	NA	NA	NA	NA	–	–	Normal	

Abbreviations: *AD* autosomal dominant, *AR* autosomal recessive, *CNS* central nervous system, *FFA* free fatty acids, *HAMA* human anti-mouse antibody, *LPL* lipoprotein-lipase, *N* normal, *NA* not affected, *r-T3* reverse T3, *SHBG* sex hormone binding globuline, *TH* thyroid hormones, *TBG* thyroxine binding globuline, *TFTs* thyroid function tests



case	TSH-oma	RTHβ
TSH 4.5 mUI/ml (0.4-5) FT4 45 pmol/l (11.5-24.5) FT3 10.3 pmol/l (2.9-7.1)	✓	✓
Young age	X	✓
BMI 20	✓	✓
Tachycardia and arrthyrmias	✓	✓
Relatives' TFTs normal	✓	X
TRH test (TSH 2.1→14mUI/L)	X	✓
SHBG 24 nmol/L (10-70)	X	✓
ICTP 215 ng/L (<580)	X	✓
Negative MRI	X	✓
Identification of a THRB variant	X	✓

ABBREVIATIONS: BMI body mass index; FDH Familial Dysalbuminemic Hyperthyroxine; HR: heart rate; ICTP carboxy-terminal telopeptide of type I collagen, MRI magnetic resonance imaging, NO-TR-RTHβ, RTHβ without mutation in the *THRB* gene; SHBG sex hormone binding globuline.

Fig. 20.1 Diagnostic flow-chart of central hyperthyroidism. A proposed flow-chart for differential diagnosis (on the left) and summary of the patient's clinical data (on the right, in the insert). The green and red arrows indicate a result compatible or non-compatible with a certain diagnosis, respectively. The red triangles represent frequent pitfalls in the diagnostic process. Abbreviations in the text. SMS-LAR somatostatin analogue long-acting-release

2. *Dynamic tests* explore the integrity of the hypothalamus-pituitary-thyroid axis and are based on the assumption that in RTHβ, the response to exogenous thyrotropin releasing hormone (TRH) is conserved, while the reduced sensitivity of the pituitary may be overcome by high TH doses. Conversely, in TSH-oma the autonomous secretion of TSH by the adenoma cannot be regulated by TRH nor contra-regulated by TH.

TRH test (i.v. injection of 200 μg of TRH with measurement of TSH at baseline and after 20′, 30′, 60′ 90′ minutes) causes a significant increase in TSH levels in normal controls and RTHβ, while no changes in TSH-omas are seen. In our patient, the TRH test showed a rise of TSH from 2.1 to 14 mIU/L 20 minutes after TRH injection (Fig. 20.1). Noteworthy, nearly 20% of the TSH-oma may respond paradoxically to TRH.

The T3 suppression test requires the administration of T3 for 10 days (fixed doses of 80–100 μg/day or increasing doses, starting with 50 and doubling every 3 days up to 200 μg/day). A complete suppression of TSH after T3 excludes a TSH-oma, whilst in RTHβ an incomplete TSH suppression may be occasionally observed. This test can be associated with a TRH test on day 10.

T3 suppression test was not performed in the case presented as it is contraindicated in patients with severe cardiac disorders, arrhythmias, and in the elderly given the risk of exacerbation of underlying cardiac problems.

In selected patients, the chronic administration of long-acting-release somatostatin analogues (SSA) every 21–28 days for 2–3 months may be helpful. TSH, FT4, and FT3 levels are measured at baseline, before each injection and 28 days after the last one. In patients with TSH-oma SSA causes a marked decrease or the normalization of FT3 and FT4 levels, while RTHβ do not respond at all.

3. *Molecular analysis* of the *THRB* gene revealed a heterozygous pathogenic variant (p.L440P) leading to the diagnosis of RTHβ. Molecular analysis makes a definitive diagnosis in 80–90% of cases. *THRB* variants are typically distributed in three "hot spot" regions of the ligand-binding domain. Mutant receptors lose their ability to modulate gene expression in target tissues and inhibit the activity of wild type receptors (the so-called dominant negative effect which explains the dominant inheritance of the disease). In 10–20% of cases with a biochemical and clinical phenotype of RTHβ, no mutation can be identified in the THRB gene and this condition is defined as "non-TR – RTH." The underlying pathogenic mechanism is still unknown.
4. *Pituitary MRI* showed a gland normal in size, signal, and dynamic contrast enhancement. However, imaging should be interpreted with caution since small pituitary lesions are common in the general population as well as in RTHβ (20–25% of magnetic resonance imaging (MRI) performed for other reasons). These lesions are considered as "pituitary incidentalomas" not associated with a hypothalamic-pituitary dysfunction. On the contrary, small micro-TSH-omas may fail to be visualized on pituitary MRI. Thyroid scintigraphy is useless because TSH-omas and RTHβ have a TSH-mediated hyperthyroidism leading to increased pertechnetate uptake in both conditions.

Are there biochemical markers indicative of RTHβ?

Basal values of carboxy-terminal telopeptide of type I collagen (ICTP) and Sex Hormone Binding Globulin (SHBG) were 215 ng/L (normal: <580) and 24 nmol/L (normal: 10–70), respectively. SHBG and ICTP are the most used markers assessing the sensitivity to TH of target tissues (liver and bone, respectively) and are expected to be normal or reduced in RTHβ and increased in hyperthyroid patients, including TSH-omas. SHBG are increased by oral contraceptives. The sensitivity and specificity of these markers improves, when assessed during a T3 suppression test.

The determination of alpha subunit of glycoprotein hormones (α-GSU) is of limited utility since levels may be normal in patients with micro-TSH-omas.

Which are the main clinical features of patients with RTHβ at presentation?

Most RTHβ patients are asymptomatic or complain of minor symptoms of thyrotoxicosis. Common features include tachycardia, hyperhidrosis, anxiety, and nervousness, while symptoms of overt thyrotoxicosis as weight loss, fatigue, heat intolerance, insomnia, and diarrhea are atypical.

At clinical assessment, fine tremors of the upper limbs, goiter, and increased heart rate (HR) are commonly observed. Body temperature and blood pressure are usually normal.

In childhood, a low body mass index (BMI) and failure to thrive are often observed, while the linear growth is not affected.

A low BMI due to increased resting energy expenditure (REE) is common also in adults and depends on muscular hyperthyroidism as suggested by the correlation between HR and REE.

Osteopenia and osteoporosis can be found even in younger patients with RTHβ.

Dyslipidemia, insulin resistance, liver steatosis, and a combined conductive and sensorineural hearing impairment have been also reported.

The patient had cardiomegaly and tachycardia. Is this common in RTHβ?

RTHβ patients exhibit palpitations and tachycardia at rest and older patients have an increased risk of atrial fibrillation. Features of hypothyroidism and hyperthyroidism coexist also at the heart level. Indeed, some indices (HR, stroke volume, diastolic filling, and maximal aortic flow velocity) have values intermediate between controls and hyperthyroid subjects, while other parameters (ejection and shortening fractions of the left ventricle, systolic diameter, and left ventricle wall thickness) are comparable to those of controls. Conversely, the increased systemic vascular resistance and increased arterial stiffness found in RTHβ are suggestive of hypothyroidism. It is noteworthy that the reduced insulin sensitivity, dyslipidemia, and liver steatosis are additional contributors worsening the overall cardiovascular risk of RTHβ.

The patient had a mood disorder. Are psychiatric manifestations common in RTHβ?

The association between mood disturbances and RTHβ is not unusual, although this anecdotal observation is not supported by large clinical studies. Some RTHβ patients have a slightly reduced IQ, while a severe mental retardation is uncommon. Nearly 30% of the school-age children may display mild learning disabilities (delayed developmental milestones and impaired verbal or performance components). Carriers of genetic variants resulting in a premature stop codon seem to have more severe cognitive disabilities. Attention deficit hyperactivity disorder (ADHD) has been reported in pediatric RTHβ patients and is thought to be caused by the low IQ more than by RTHβ per se.

Which investigations may be useful in the follow-up of RTHβ patient?

Thyroid US scan should be periodically performed to monitor thyroid nodules and cytology is needed in case of growing or suspicious thyroid nodules. Although some cases of papillary thyroid cancers are reported in RTHβ patients, and mice harboring a knock-in dominantly negative mutation of the TRβ ($TR\beta^{PV/PV}$) spontaneously develop follicular thyroid carcinoma, it is unclear if RTHβ increases risk of malignancy.

A cardiovascular assessment should be regularly performed, and echocardiography is indicated at diagnosis, as an increased frequency of valvular heart disease has been reported by some authors.

A 24-hour Holter ECG monitoring is useful when asymptomatic atrial fibrillation is suspected, or an ECG diagnosis of unexplained arrhythmic symptoms is warranted.

Bone densitometry by dual-energy x-ray absorptiometry (DEXA) is indicated as osteopenia and osteoporosis are common in RTHβ.

In patients with AITD a careful monitoring of TFTs and of patients' symptoms is required in order to promptly recognize and treat acquired thyroid dysfunctions.

Are there other forms leading to RTH?

Other syndromes associated with resistance to TH can be easily differentiated from RTHβ due to the different clinical manifestations as shown in Table 20.1.

RTHα is caused by heterozygous dominant negative mutations in the TRα receptor. FT4 levels are normal or slightly reduced, while FT3 levels are above the upper level

of normal, resulting in a reduced FT4/FT3 ratio. These patients exhibit features of untreated congenital hypothyroidism in tissue expressing the TRα.

- Genetic defects of monocarboxylate transporter 8 (MCT8) causes the X-linked mental retardation or Allan-Herndon-Dudley syndrome associated with a severe neurological phenotype. MCT8 is the main transporter of TH into neurons and inactivation of this transporter results in impaired central nervous system (CNS) development. Serum FT3 levels are very high, whereas FT4 and rT3 concentrations are typically reduced. TSH levels are often high suggesting T3 insensitivity at hypothalamic-pituitary level. Conversely peripheral tissues, expressing other transporters, are thyrotoxic as suggested by the high levels of SHBG, the low levels of cholesterol and the muscle wasting.

- Mutations in SECIS-binding protein 2 (SBP2), a key protein that allows the incorporation of selenium in selenoproteins, cause defective function of the deiodinases involved in TH metabolism. This defect results in an abnormal pattern of TFTs characterized by high free T4, low free T3, raised reverse T3, associated with normal or slightly elevated TSH levels. The phenotype of the disease is complex, because selenoproteins are ubiquitous and multifunctional. Affected individuals manifest growth retardation, axial muscle dystrophy, azoospermia, anemia, lymphopenia, increased adipose mass, increased insulin sensitivity, and high-frequency hearing loss.

What kind of treatment should be proposed?

- The goal of the treatment is the relief of the symptoms, as no treatments are available to correct these molecular defects.

- Beta receptor blockers (bisoprolol and atenolol) well controlled tachycardia in our patient but were discontinued because of skin reactions and hypotension. When β-blockers are contraindicated or thyrotoxic symptoms persists, a reduction of TH levels may be beneficial. This can't be achieved using antithyroid drugs, because the consequent increase of the TSH causes a goiter enlargement and pituitary hyperplasia.

- Conversely, the administration of the thyromimetic triiodothyroacetic acid (TRIAC) is the treatment of choice in these cases. TRIAC is also beneficial in RTHβ children with ADHD. TRIAC (therapeutic range: 1.4–2.8 mg/day) reduces TSH secretion through the feedback mechanism and TH synthesis; in addition, its effects are weaker than that of T3, thus reducing the thyrotoxic manifestations.

- During treatment TSH and FT4 are measured for dose adjustment, while FT3 is unreliable as TRIAC cross reacts with T3 in most of the assays.

- In our patient TRIAC improved tachycardia with no adverse events during a two-year follow-up. Hyperhidrosis persisted and required botulinum toxin injections.

- The management of osteoporosis should be the same as in the general population, since it is unclear if RTHβ increases the risk of fracture. The treatment of additional risk factors (such as smoking, vitamin D deficiency, inadequate calcium intake with the diet, and idiopathic hypercalciuria) improves bone mineral density in most of the RTHβ patients.

- TRβ selective agonists are promising drugs for RTHβ patients. Resmetirom (presently under investigation in a phase 3 study in euthyroid patients affected with non-alcoholic fatty liver disease) might be used in the future for treating liver steatosis and dyslipidemia in RTHβ. Unfortunately, the effects of this drug are limited to the liver, thus is not expected to correct central hyperthyroidism at the pituitary level.

The patient has an associated Hashimoto thyroiditis. How an acquired primary hypothyroidism can be managed in a patient affected with RTHβ?

Supraphysiological doses of levothyroxine are necessary in RTHβ patients being hypothyroid because of an associated autoimmune thyroid disease or after thyroid ablation for a missed diagnosis of RTHβ. Levothyroxine replacement treatment requires a careful monitoring, assessing not only the TSH, but also peripheral markers of TH action.

As this patient was on TRIAC, the progression toward hypothyroidism can be suspected if increasing doses of TRIAC are needed to maintain the TSH within the normal range. In this case TRIAC can be discontinued and levothyroxine can be started; alternatively TRIAC and levothyroxine can be combined if thyrotoxic symptoms persist on levothyroxine monotherapy.

Is thyroid surgery indicated in RTHβ patients?

Thyroid surgery should be reserved to patients with malignancies or large goiters compressing the airways. Levothyroxine treatment often fails to maintain the TSH in the preoperative range because of the appearance of thyrotoxic symptoms, thus in patients needing TSH-suppressive treatment (e.g., differentiated thyroid cancer), levothyroxine may be combined with TRIAC.

Lobectomy/subtotal thyroidectomy should be avoided, as the goiter commonly relapses, with nodular alterations and gross asymmetries, requiring additional surgery or radioiodine.

Tips

The reader is advised to read the chapter on Graves' disease (hyperthyroidism) (► Chap. 12). Macroprolactinemia that is a phenomenon analogous to macro-TSH is discussed in the chapter on Prolactinoma (► Chap. 1).

Take Home Messages

- RTHβ is a rare autosomal dominant disease causing central hyperthyroidism.
- The suspicion for the disease can be raised based on the biochemical feature of inappropriate secretion of TSH, but a genetic diagnosis is needed to confirm the disease.
- Patients are often asymptomatic or may exhibit variable symptoms of thyrotoxicosis in tissues mainly expressing the TRα as the heart (increased heart rate), skeletal muscle (increased resting energy expenditure), and the bone (osteopenia/osteoporosis).
- A correct differential diagnosis between RTHβ and TSH-oma is mandatory to avoid useless and even dangerous treatment such as unnecessary pituitary surgery.
- Treatment is aimed at controlling thyrotoxic symptoms.
- Thyroid surgery is indicated only in case of malignancies or large compressive goiter.

Suggested Reading

1. Beck-Peccoz P, Lania A, Beckers A, Chatterjee A, Wemeau JL. 2013 European thyroid association guidelines for the diagnosis and treatment of thyrotropin-secreting pituitary tumors. Eur Thyroid J. 2013;2(2):76–82. https://doi.org/10.1159/000351007.
2. Dumitrescu AM, Refetoff S. Impaired sensitivity to thyroid hormone: defects of transport, metabolism and action, In: Feingolt KR, Anawalt B, Boyce A, et al., editors. South Dartmouth (MA): MDText.com. Available at www.endotext.org Last updated: 20 August 2015.
3. Koulouri O, Moran C, Halsall D, Chatterjee K, Gurnell M. Pitfalls in the measurement and interpretation of thyroid function tests. Best Pract Res Clin Endocrinol Metab. 2013;27(6):745–62. https://doi.org/10.1016/j.beem.2013.10.003.
4. Persani L, Campi I. Syndromes of resistance to thyroid hormone action. Exp Suppl. 2019;111:55–84. https://doi.org/10.1007/978-3-030-25905-1_5.
5. Refetoff S, Bassett JH, Beck-Peccoz P, Bernal J, Brent G, Chatterjee K, De Groot LJ, Dumitrescu AM, Jameson JL, Kopp PA, Murata Y, Persani L, Samarut J, Weiss RE, Williams GR, Yen PM. Classification and proposed nomenclature for inherited defects of thyroid hormone action, cell transport, and metabolism. Eur Thyroid J. 2014;3(1):7–9. https://doi.org/10.1159/000358180.
6. Schoenmakers E, Agostini M, Mitchell C, Schoenmakers N, Papp L, Rajanayagam O, Padidela R, Ceron-Gutierrez L, Doffinger R, Prevosto C, Luan J, Montano S, Lu J, Castanet M, Clemons N, Groeneveld M, Castets P, Karbaschi M, Aitken S, Dixon A, Williams J, Campi I, Blount M, Burton H, Muntoni F, O'Donovan D, Dean A, Warren A, Brierley C, Baguley D, Guicheney P, Fitzgerald R, Coles A, Gaston H, Todd P, Holmgren A, Khanna KK, Cooke M, Semple R, Halsall D, Wareham N, Schwabe J, Grasso L, Beck-Peccoz P, Ogunko A, Dattani M, Gurnell M, Chatterjee K. Mutations in the selenocysteine insertion sequence-binding protein 2 gene lead to a multisystem selenoprotein deficiency disorder in humans. J Clin Invest. 2010;120(12):4220–35. https://doi.org/10.1172/jci43653.
7. Socin HV, Chanson P, Delemer B, Tabarin A, Rohmer V, Mockel J, Stevenaert A, Beckers A. The changing spectrum of TSH-secreting pituitary adenomas: diagnosis and management in 43 patients. Eur J Endocrinol. 2003;148(4):433–42. https://doi.org/10.1530/eje.0.1480433.
8. van Gucht ALM, Moran C, Meima ME, Visser WE, Chatterjee K, Visser TJ, Peeters RP. Resistance to thyroid hormone due to heterozygous mutations in thyroid hormone receptor alpha. Curr Top Dev Biol. 2017;125:337–55. https://doi.org/10.1016/bs.ctdb.2017.02.001.

Hyper- and Hypothyroidism in Pregnancy, Postpartum Thyroiditis

Miklós Bodor

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_21

Opening

In this chapter the pregnancy-related clinical features of the most common thyroid diseases, namely hyper- and hypothyroidism, will be discussed along with the most frequent thyroid illness after delivery, the postpartum thyroiditis.

21.1 Hyperthyroidism in Pregnancy

Definition of the Disease

Gestation resembles hyperthyroidism due to a physiological enlargement of the thyroid gland and increase in the cardiac output. Due to the elevated thyroid binding protein (TBG) level, the amount of total blood thyroxine increases; however, the free thyroid hormones, the free thyroxine index, and TSH levels remain within the normal range.

Temporary or permanent impairment in the thyroid function resulting in hyperthyroidism affects 2–3% of all pregnancies. The most common form is the transient gestational thyrotoxicosis (TGT), which does not need therapy in most of the cases. The significantly increased amount of human chorionic gonadotropin (hCG) in the blood can bind to the TSH receptor due to a great homology in both the hormones and receptors. In TGT, no thyroid-associated antibodies are present. Typically, TGT does not require specific therapy, short time β adrenerg receptor blocker administration may be considered, and treatment with antithyroid medication is very rarely needed.

It is noteworthy that the hCG-induced physiological decrease in the serum TSH of pregnant women does not need therapy (usually observed between the 6th and 15th weeks of pregnancy).

True elevation of the free thyroid hormones T3 and T4 along with suppressed TSH complicates 0.1–0.2% of gestations. Overt hyperthyroidism mildly enhances the risk of abortion and is associated with a higher risk of early delivery in 11–25% of pregnancies.

The most frequent cause of gestational hyperthyroidism is Graves' disease (GD), where antibodies against the TSH receptor are responsible for the maintenance of the thyrotoxicosis. The detailed description and treatment of the disease is discussed in ► Chap. 12, and only specific considerations in pregnancy are detailed in this section.

The immunological changes during pregnancy attenuate the course of GD, and the symptoms usually ameliorate after the first semester. The clinical diagnosis of the disease might be difficult because the regularly occurring gestational symptoms might overlap with the complaints caused by the mild hyperthyroidism.

Other diseases causing hyperthyroidism (toxic adenoma, toxic multinodular goiter, subacute thyroiditis, hydatidiform mole, and iatrogenic hyperthyroidism) are very rare in pregnant women.

Case Presentation 1

A 32-year old patient treated for Graves' disease presented to our endocrinology clinic having a 6-week pregnancy confirmed by her gynecologist. She was diagnosed with the illness 5 months ago upon characteristic symptoms and high TRab (TSH receptor antibody) level. Treatment with methimazole was initiated, and at the time she took 20 mg daily. Her heart rate was 66/min. The thyroid was slightly enlarged by palpation and no nodules were

present. The thyroid ultrasound performed at the time of diagnosis showed mildly enlarged thyroid lobes, hypervascularity, and nodules were not detected. Recent laboratory findings: TSH: 0.9 (normal 0.3–4.2 mIU/L), FT4: 17.2 (normal 12–22 pmol/L), FT3: 4.1 (normal 2.4–6.3 pmol/L). She had no complaints other than frequently occurring mild morning nausea.

Are there additional tests to perform?

A repeated measurement of serum TRab should be performed since the TSH stimulating IgG antibody penetrates the placenta through active transport and can cause goiter in the fetus as well as neonatal thyrotoxicosis. The titer of the TRab usually decreases during gestation, and its level should be measured in the first trimester and again in the 6th month of the pregnancy.

Is the treatment adequate?

No. Both thyroid peroxidase-blocking agents methimazole and propylthiouracil are appropriate for the treatment of non-pregnant patients with GD; however, administration of methimazole, mostly during the first trimester, can lead to increased risk of fetal esophagus atresia, growth retardation, and aplasia cutis. According to the current guidelines, during the first trimester propylthiouracil should be preferred, being considered reasonably safe in doses of 300 mg daily or less. The serum FT4 level should be adjusted to the upper-normal level, and cessation of medication can be attempted at the end of the second trimester; however, even applied at low doses, newborns might develop a detectable goiter in about 10% of cases. The block-replacement therapy is contraindicated since it may mask the fetal hypothyroidism. The propylthiouracil treatment can be continued during the second and third trimesters; however, switching back to methimazole is also permitted. In case of women with GD who are planning to get pregnant, switching to propylthiouracil is strongly advised. Nevertheless, it is advised that pregnancy should not be planned in women with poorly controlled hyperthyroidism. If euthyroidism is attained on a stable therapy, two normal hormonal results in a 2 month period can be proposed to precede pregnancy.

Are there any other specific measures to be considered?

The pregnant GD patient should be regularly followed up by a team consisting of an endocrinologist, a gynecologist and, if needed, an ophthalmologist. Although endocrine orbitopathy (EO) usually ameliorates during gestation due to the physiologically suppressed immune system, in case of previously or newly detected EO, adequate treatment might be initiated (▶ Chap. 14).

The gynecologist should follow the pregnant patient regularly with ultrasound and be aware of possible signs of fetal hyperthyroidism (tachycardia with heart rate above 160/min., goiter visible on echography that may cause tracheal obstruction).

Are any other treatment options in gestational hyperthyroidism caused by GD?

Radioiodine therapy is strictly contraindicated. Total or partial thyroidectomy is an option in case of drug allergy or serious non-compliance and can be safely carried out in the second trimester with a slightly increased risk of preterm delivery.

Are there any specific considerations in the management of the newborn?

The newborns should be meticulously observed. Neonates of mothers being on propylthiouracil therapy might need levothyroxine supplementation. The TRab caused by the mother's GD can induce GD in the infant that may last for up to 2 weeks and requires transient intensive care.

Management of the mother's GD after delivery

Breast-feeding is not contraindicated during propylthiouracil medication (up to 150 mg/day), which is the preferred therapy because it is secreted in a lesser amount into the breast milk than methimazole.

21.2 Hypothyroidism in Pregnancy

Definition of the Disease

The serum TSH is the most sensitive marker for the evaluation of thyroid function. In subclinical hypothyroidism, TSH is already slightly elevated while the free hormones remain within the normal range. Fertility is reduced even in the subclinical form, and overt hypothyroidism is uncommon in pregnancy since most women with this type of thyroid dysfunction often have anovulation. The prevalence of subclinical hypothyroidism in developed countries is 2–3%, while clinical hypothyroidism occurs in 0.3–0.5% of pregnancies. In Europe and the USA, the most frequent cause of thyroid hypofunction is autoimmune thyroiditis, but hypothyroidism may develop also after thyroid surgery or radioiodine therapy. In developing countries, iodine deficiency is still responsible for the vast majority of gestational hypothyroidism. In this case the clinical presentation is usually less symptomatic, but the complications might be severe: hypertension, preeclampsia, miscarriage, postpartum bleeding, abortion, low birth weight, and intellectual cognitive deficit may occur. The most important period for the intrauterine central nervous system development is between 6 and 24 gestational weeks, the insufficient maternal thyroid hormone levels can cause irreversible brain injury. With adequate L-thyroxine substitution these consequences can be avoided.

It is of major importance to optimize thyroid function in hypothyroid women before pregnancy.

Case Presentation 2

A 26-year old woman with freshly recognized pregnancy in her sixth gestational week presented to the endocrinology with a history of treated Hashimoto's hypothyroidism for 2 years, currently taking daily 75 ug levothyroxine. At the time she was in her sixth gestational week. The previous diagnosis was made upon clinical hypothyroidism and elevated aTPO (anti-thyroid peroxidase antibody) level. The last thyroid hormone check-up was done 2 months ago; at the time TSH was 2.9 (normal 0.3–4.2 mIU/L). The most recent thyroid ultrasound was performed 5 months ago showing slightly smaller lobes with two known small nodules, being 5 and 7 mm, which did not change in size during the previous follow-ups. She had no complaints at the time of presentation.

Are there additional tests to perform?

Yes. The thyroid function should be evaluated as soon as the pregnancy is recognized. Also, although in males and non-pregnant women, monitoring of TSH alone is sufficient for the adjustment of levothyroxine substitution, due to the

previously discussed physiological changes in serum TBG and the effect of hCG, the TSH value per se does not give sufficient information, the measurement of the free thyroid hormones are also recommended.

The thyroid tests performed showed TSH: 4.1 (normal 0.3–4.2 mIU/L), FT4: 13.2 (normal 12–22 pmol/L), and FT3: 3.8 (normal 2.4–6.3 pmol/L).

Is the treatment adequate?

No. During the treatment of hypothyroidism during gestation the trimester-specific alterations in thyroid physiology and metabolism must also be considered. The TSH range for each trimester, according to the current guidelines, is as follows: 0.1–2.5 mIU/L for the first trimester, 0.2–3.0 mIU/L for the second trimester, and 0.3–3.0 mIU/L for the third trimester. The daily needed L-thyroxin dose in non-pregnancy is around 1.6 μg/kg which increases during gestation to 1.9 μg/kg. During pregnancy, the levothyroxine dose should be increased by 25–30%.

In our patient, the slightly increased TSH level is a response to the growing demand for maternal levothyroxine. As a result, the dose should be increased to 100 μg daily levothyroxine administration.

Is it needed to measure anti-thyroid peroxidase antibody (aTPO) again and to repeat thyroid ultrasound?

There is no need to remeasure the aTPO level because the result has no effect on the therapy. Since there is no evidence that thyroid nodules might enlarge during pregnancy, there is no need to perform a thyroid ultrasound examination.

How often should the thyroid status be checked?

In case of known hypothyroidism, checking the thyroid function immediately after the recognition of gestation and regularly every 4–6 weeks until delivery is necessary. The TSH should be adjusted according to the above detailed recommendations.

How should be the mother's hypothyroidism managed after delivery?

After delivery, the levothyroxine substitution can be decreased to the initial dose administered before pregnancy, and the routine follow-ups should be performed every 6 months. Our patient was advised to take again 75 ug levothyroxine daily.

21.3 Postpartum Thyroiditis

Definition of the Disease

Postpartum thyroiditis (PPT) is the occurrence of thyroid dysfunction (GD excluded) during the first postpartum year in women who were euthyroid before pregnancy. PPT has an average prevalence of approximately 5–9% of pregnancies, ranging from 1% to 22% according to the literature. The rate is lower in iodine-depleted regions, while in iodine well-supplemented countries more PPT cases are noticed. Because of its autoimmune nature, other autoimmune diseases might predispose for PPT or may appear later in the affected patients. The most significant disease as risk factor is type 1 diabetes, in which the probability for developing PPT in the future is 25%. Other autoimmune disorders such as Sjögren's syndrome, systemic lupus erythematosus, chronic viral hepatitis, multiple sclerosis, and antipituitary antibodies positivity were found to be also risk factors for developing PPT. Serum positivity for thyroid autoantibodies aTPO and thyroglobulin antibody (TgAb) during pregnancy represent a major risk for the development of PPT. The

aTPO positivity is the best marker to predict PPT. 33–50% of antibody-positive pregnant women will develop the disease, on the other hand, in case of aTPO negativity the incidence is very low. The probability for developing PPT in case of aTPO and/or TgAb during gestation is much higher than the risk for other complications.

The clinical picture of PPT resembles that of subacute thyroiditis (► Chap. 16); however, thyroid tenderness and anterior neck pain are absent. The classic form of PPT has three phases similar to that of subacute thyroiditis: first a transient hyperthyroidism lasting for 8–24 weeks postpartum is seen, which is followed by a stage of hypothyroidism (3–12 months postpartum) and finally by a euthyroid state usually by the end of the first year after delivery. About 25% of women present the classical form, but in 25% of cases only thyrotoxicosis is present, and one half of the patients develop only isolated hypothyroidism. After subsequent pregnancies, the disease often returns. In approximately half of PPT women hypothyroidism will become permanent.

The diagnosis depends on the actual phases of the disease. During the initial phase, TSH is suppressed with elevated serum FT4 and FT3. In this case, differentiation of PPT from GD is important.

A suggested algorithm for the treatment and monitoring of PPT is presented in ◘ Fig. 21.1.

Case Presentation 3

A 27-year-old woman presented to our endocrinology clinic 3 months after her first delivery. She complained of heat intolerance, fatigue, and palpitations. She was breast-feeding. The thyroid was slightly enlarged by palpation, and no tenderness nor nodules were present.

What laboratory tests should be performed?

The most common cause of the above symptoms in our case is PPT. To confirm the diagnosis, functional thyroid tests are needed. The results were as follows: TSH: 0.2 (normal 0.3–4.2 mIU/L), FT4: 31.2 (normal 12–22 pmol/L), FT3: 6.2 (normal 2.4–6.3 pmol/L). aTPO: 231 (normal <16 IU/mL), TRab was negative. Heart rate was 98/min. According to the results PPT was confirmed.

In GD, the TRab level is elevated, and it is typically negative in PPT. An elevated T4:T3 ratio suggests the presence of PPT. The clinical signs of GD (goiter and orbitopathy) are diagnostic if present. The radioiodine uptake is enhanced in GD and decreased in the thyrotoxic phase of PPT, but the use of radioactive diagnostics in breast-feeding patients is contraindicated. Due to its short half-life technetium scintigraphy (^{99m}Tc) can cautiously be performed in lactating women if breast milk is discarded for three days after the procedure was done.

Thyroid ultrasound is not needed for the diagnosis; however, a thyroid echography within six months might be beneficial for the detection of unpalpable nodules.

Is any treatment necessary?

Since the initial phase of PPT is characterized by transient hyperthyroidism, and the symptoms are typically mild, treatment should be initiated only when the patient's complaints are severe. Antithyroid drugs (methimazole and propylthiouracil) are ineffective because PPT is a destructive thyroiditis and the thyroid hormone synthesis

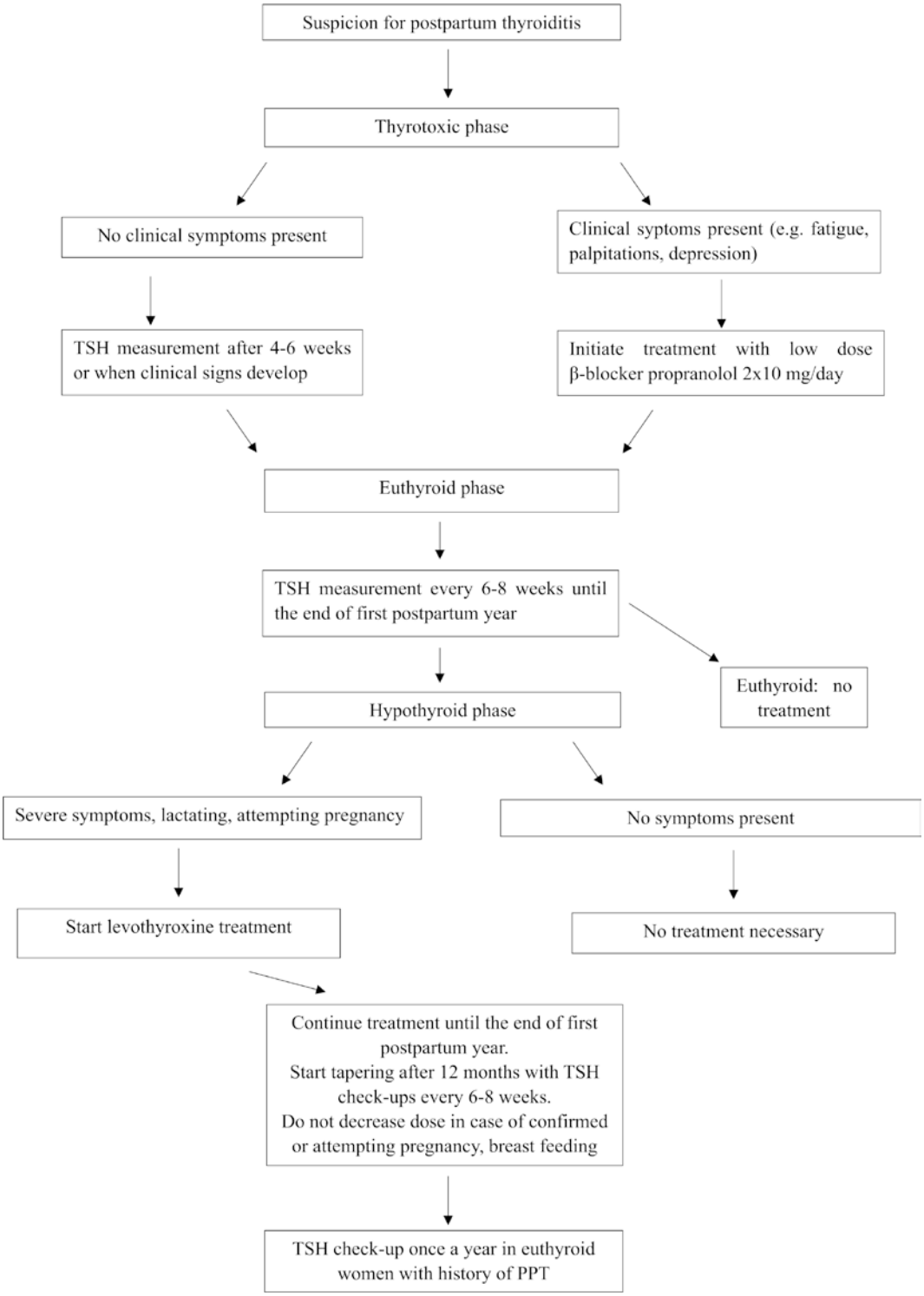


Fig. 21.1 Algorithm for the treatment and monitoring of postpartum thyroiditis

is absent or diminished. Among β-blockers, propranolol or metoprolol are safe for breast-feeding women and should be administered at the lowest possible dose to improve the symptoms. The therapy is usually required for only a few weeks and can be stopped after the symptoms ameliorate.

In the present case 10 mg propranolol was initiated two times daily.

How often should the thyroid status be checked?

The thyroid hormones need to be measured after 4–8 weeks to screen for the second, hypothyroid phase.

In our patient, the laboratory tests were the following after 4 weeks: TSH: 1.9 (normal 0.3–4.2 mIU/L), FT4: 18.4 (normal 12–22 pmol/L), FT3: 4.2 (normal 2.4–6.3 pmol/L). Heart rate: 64/min. The therapy with the β-blocker propranolol was stopped accordingly.

After an additional 5 weeks the TSH became 2.3 (normal 0.3–4.2 mU/L) with a concomitant FT4: 15.7 (normal 12–22 pmol/L) and FT3: 3.9 (normal 2.4–6.3 pmol/L).

Does the hypothyroid phase need treatment?

In case of postpartum women whose symptoms are significant, and are breast-feeding or considering another conception, levothyroxine supplementation should be started. The thyroid status needs follow-up every 4–8 weeks.

Once started, how long should the treatment be continued?

The bottom line is to avoid hypothyroidism and maintain normal thyroid hormone levels, especially in women who are attempting pregnancy. The medication can be tapered after the first year postpartum to check whether the hypothyroid phase was just transient or will persist. The decrease in levothyroxine dose should be gradual and the thyroid function needs monitoring every 6–8 weeks.

After cessation of the hypothyroid phase how often should the thyroid function be checked?

Ten to fifty percent of women with PPT in whom the hypothyroid phase resolves will eventually acquire permanent hypothyroidism. Hypoechogenicity on thyroid ultrasound, multiparity, severe hypothyroidism during the second phase, high aTPO titers, and history of abortion or higher maternal age are predisposing factors. The thyroid hormones should be checked annually in women who previously developed PPT.

Are there any treatments that might prevent the development of PPT in euthyroid, thyroid antibody positive pregnancy?

There is no evidence that either iodine or levothyroxine treatment would prevent the development of PPT in aTPO or TgAb positive pregnant women. The benefit of supplementation with selenium was not unequivocally confirmed, furthermore, the use of selenium was linked to an increased risk of type 2 diabetes. Overall, the treatment with levothyroxine or iodine in case of thyroid antibody positive but euthyroid pregnant women is not recommended, nor is selenium supplementation.

Tips

- The reader is advised to read the chapters on hypo- and hyperthyroidism (▶ Chaps. 11 and 12), the chapter on endocrine orbitopathy (▶ Chap. 14) and subacute (de Quervain) thyroiditis (▶ Chap. 16).

Take Home Messages

- The diseases of the thyroid gland during pregnancy and the postpartum period are common, affecting 1–20% of women.
- The most common cause of gestational hyperthyroidism is Graves' disease, where the elevated TSH receptor antibodies cause thyrotoxicosis.
- The thyroid peroxidase-blocking propylthiouracil is safe and advisable for the treatment of hyperthyroidism caused by Graves' disease during the first trimester; β-blockers as adjuvant therapy may be needed.
- The most frequent cause of thyroid hypofunction during pregnancy in the developed countries is autoimmune thyroiditis.
- The demand for levothyroxine in pregnancy increases by 25–30%, so in treated hypothyroidism the levothyroxine dose should be adjusted accordingly, and after delivery the dose can be reduced to the initial regimen.
- Postpartum thyroiditis affects up to one-fifth of women after delivery, positive anti-TPO during pregnancy is the most important risk marker.
- The disease typically has a three-phase course, and the therapy depends upon the time of recognition and severity of symptoms; β-blockers or hormone substitution should be started depending on the hyper- or hypothyroid phase, respectively.

Suggested Reading

1. Belucan FS, Morshed SA, Davies TF. Thyroid autoantibodies in pregnancy: their role, regulation and clinical relevance. J Thyroid Res. 2013;2013:182472. https://doi.org/10.1155/2013/182472.
2. Benvenga S, Vita R, Di Bari F, Le Donne M, Triolo O, Granese R, Borrielli I, Sole G, Floridia M, Genovesi F, Tromba D, Tromba D. Relatively high rate of postpartum thyroiditis in the Straits of Messina area. Predictivity of both postpartum thyroiditis and permanent hypothyroidism by performing, in the first trimester of gestation, thyroid ultrasonography and measurement of serum thyroperoxidase and thyroglobulin autoantibodies. J Clin Transl Endocrinol. 2019;15:12–8. https://doi.org/10.1016/j.jcte.2018.11.004.
3. Di Bari F, Granese R, Le Donne M, Vita R, Benvenga S. Autoimmune abnormalities of postpartum thyroid diseases. Front Endocrinol. 2017;8:166. https://doi.org/10.3389/fendo.2017.00166.
4. Kahaly GJ, Bartalena L, Hegedüs L, Leenhardt L, Poppe K, Pearce SH. 2018 European Thyroid Association guideline for the management of graves' hyperthyroidism. Eur Thyroid J. 2018;7:167–86.
5. Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R, Vaidya B. 2014 European Thyroid Association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. Eur Thyroid J. 2014;3(2):76–94. https://doi.org/10.1159/000490384.
6. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, Nixon A, Pearce EN, Soldin OP, Sullivan S, Wiersinga W, American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid. 2011;21(10):1081–125. https://doi.org/10.1089/thy.2011.0087.

Diseases of the Parathyroid and Metabolic Bone Diseases

The parathyroid glands are located in the vicinity of the thyroid, but their hormone secretion is not regulated by the pituitary. Parathyroid glands secrete parathyroid hormone that is the pivotal regulator of calcium homeostasis. Primary hyperparathyroidism due to the autonomous overproduction of parathyroid hormone became the third most common endocrine abnormality due to the widespread introduction of routine serum calcium measurements. In many cases, it manifests itself as a mild asymptomatic hypercalcemia; however, severe morbidity can also occur (► Chap. 22). Secondary and tertiary hyperparathyroidism is also briefly discussed in ► Chap. 22. In contrast, hypoparathyroidism is rare (► Chap. 23), but the resulting hypocalcemia can be associated with major clinical relevance. Metabolic bone diseases including osteoporosis (► Chap. 24) and osteomalacia (► Chap. 25) are among the most common diseases that affect a significant proportion of the population.

Contents

Primary Hyperparathyroidism

Judit Tőke

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_22

Opening

In this chapter, the reader will get acquainted with the clinical features, diagnosis, and treatment of primary hyperparathyroidism. Secondary and tertiary hyperparathyroidism are also briefly discussed. Humoral hypercalcemia of malignancy and the treatment of hypercalcemia are discussed in a different chapter.

Definition of the Disease

Primary hyperparathyroidism (PHPT) is related to the autonomous hypersecretion of parathyroid hormone (PTH) from one or more of the four parathyroid glands. The majority of all cases are sporadic; however, there are some genetic syndromes in which PHPT could occur. Nowadays the vast majority of patients are asymptomatic, and the classical skeletal and renal symptoms of PHPT are rarely seen. The incidence of the disease is approximately 25–50/100.000 person/year with peaks between the age of 50 and 60 years. Primary hyperparathyroidism is the third most common endocrine disease following diabetes mellitus and hypothyroidism. Women are affected 2–4 times more commonly than men.

Case Presentation

A 48-year-old man was referred to our endocrine consultation. His investigations started because of recurring left lower abdominal pain. Routine laboratory tests revealed moderate hypercalcemia therefore he was suggested to have endocrine consultation.

He has been treated for hypertension for 20 years and a renal stone in the left kidney was treated with extracorporal shock wave lithotripsy 5 years before his admission. Family history included hypertension in his father and osteoporosis in her mother. His younger sister and his two children are known to be healthy.

What are the investigations needed to determine the cause of hypercalcemia?

Detailed laboratory tests are recommended in patients with hypercalcemia. Measurement of serum concentration of total and ionized calcium, phosphate, parathyroid hormone, 1,25-dihydroxy-vitamin D, and biochemical markers of bone metabolism (osteocalcin and β-crosslaps) as well as determining urinary calcium excretion are essential to have a deeper insight into the calcium homeostasis of a hypercalcemic patient. Drugs which could influence serum calcium level (e.g., thiazide diuretics and lithium that reduce urinary Ca-excretion and thereby can increase serum calcium) should be discontinued if possible for the correct interpretation of the laboratory results. It is also important to ensure that the patient is not restricting dietary calcium. The diagnosis of primary hyperparathyroidism can be usually unambiguously established based on its characteristic biochemical hallmark of elevated serum calcium levels and inappropriately normal or high serum parathyroid hormone levels. Serum phosphate concentration is usually decreased, 1,25-dihydroxy-vitamin D is usually moderately low, while serum β-crosslaps concentration reflecting to bone resorption is typically high. Despite high parathyroid hormone concentration, hypercalcemia leads to high urinary calcium excretion (>8–10 mmol/day). In contrast with osteomalacia resulting from vitamin D deficiency, serum alkaline phosphatase levels are usually normal.

The laboratory results of the patient and the normal ranges of the parameters are presented in Table 22.1.

What kinds of other disorders are important to consider in the differential diagnosis of PTH-dependent hypercalcemia?

Inactivating mutations of the calcium-sensing receptor (*CaSR*) gene lead to

Table 22.1 Laboratory results of the patient and normal ranges of Ca-related parameters

Laboratory test	Reference range	Result at diagnosis	Result at the beginning of the operation	Result 10 minutes after tumor resection	Result 6 months after the operation
Serum calcium (mmol/L) Serum calcium (mg/dL)	2.20–2.65 8.82–10.62	3.17			2.47
Serum ionized calcium (mmol/L) Serum ionized calcium (mg/dL)	1.05–1.25 4.21–5.01	1.62			1.20
Serum phosphate (mmol/L)	0.81–1.45	0.85			0.97
Serum parathyroid hormone (pg/mL) Serum parathyroid hormone (pmol/L)	10–85 1.06–9.01	306	368	89	80
Serum albumin (g/L)	35–52	44.7			43.9
Serum 25-OH-Vitamin D (ng/mL)	30–60	40.4			34.9
Serum creatinine (μmol/L)	59–104	80			64
Urinary calcium (mmol/24 h)	2.5–7.5	18.0			6.02
GFR (mL/min/1.73 m^2)	90–120	>90			>90
CaCrCR		0.021			0.007

GFR Estimated Glomerular Filtration Rate, *CaCrCR* Calcium to creatinine clearance ratio

pathological resistance to the rising ionized calcium concentration in the extracellular space manifesting itself in diverse disease states in humans.

Familial hypocalciuric hypercalcemia type I (FHH1, OMIM: 145980) is caused by germline heterozygous, loss-of-function *CaSR* gene mutations on chromosome 3q21.1 FHH1 is characterized by mild, non-progressive hypercalcemia, normal (in 80% of cases) or slightly elevated (in 20% of cases) serum parathyroid hormone levels and hypocalciuria described by low (<0.01) calcium to creatinine clearance ratio (CaCrCR). The life-long mild hypercalcemia is symptomless in the majority of patients.

Although certainly not raising a differential diagnostic problem in an adult patient, neonatal severe hyperparathyroidism (NSHPT, OMIM: 239200) should be mentioned here that is caused by homozygous or compound heterozygous inactivating mutations of the *CaSR* gene. The clinical manifestation may be life-threatening as severe hypercalcemia (>3.5 mmol/L), respiratory distress, hypotonia, and spontaneous bone

fractures could develop in the affected neonates. Parathyroidectomy would serve as a reasonable therapeutic option.

Is it important to consider the CaSR disorders in the diagnosis of PHPT?

In clinical practice, FHH should be differentiated from mild forms of primary hyperparathyroidism (PHPT) as parathyroidectomy indicated for PHPT will not improve hypercalcemia in FHH patients. The differential diagnosis is usually simple by determining calcium: creatinine clearance ratio. The calculation of CaCrCR is based on this formula:

- 24-h urinary calcium (mmol/L) × serum creatinine (μmol/L)
- 24-h urinary creatinine (μmol/L) × serum calcium (mmol/L)

What kinds of evaluations are recommended in patients diagnosed with PHPT?

Nowadays, PHPT is usually discovered incidentally as biochemical screening tests including serum calcium and phosphate measurements became routinely employed. Consequently, the vast majority of newly diagnosed patients (80%) have asymptomatic hypercalcemia. However, patients are recommended to be screened for several complications affecting the key target organs of parathyroid hormone action: kidney and bone.

In patients with PHPT, three-site dual energy X-ray absorptiometry should routinely be obtained (lumbar spine, hip, and one-third distal radius). Interestingly, the bone mineral density (BMD) of the distal one-third radius, a site of cortical bone, will typically be low, while BMD in lumbar spine and femoral neck could be normal. If clinicians miss the measurement of distal radius, bone loss could remain undiagnosed.

To assess kidney function, routine serum laboratory tests (creatinine, urea nitrogen, and glomerular filtration rate) and 24-h urine collection are necessary to determine calcium excretion. If hypercalciuria is present, stone risk profile analysis with commercially available laboratory kits is recommended. Abdominal imaging (computed tomography [CT] or ultrasound) could help to detect nephrocalcinosis and asymptomatic nephrolithiasis.

Regarding our patient's results, we detected osteopenia at all three measured sites; however, t-score value was characteristically the lowest at the distal 1/3rd of non-dominant radius (t-score values were: 0.00, −0.90, −2.00 on the lumbar spine, femoral neck and distal one-third radius, respectively). Vertebral fractures have not been revealed with vertebral fracture assessment. Abdominal ultrasound showed bilateral nephrocalcinosis.

What are the symptoms related to parathyroid hormone excess?

Symptoms of PHPT are usually seen when the disease remains undiagnosed for a long time or when the pathologically high parathyroid hormone excess progresses rapidly. The signs and symptoms may include the effect of hypercalcemia itself and the impairment of target organs of parathyroid hormone (bone and kidney).

Symptoms of hypercalcemia depend on its severity, on the elapsed time from the beginning and on the rate of its development. Nephrogenic diabetes insipidus presenting with polyuria, polydipsia, as well as constipation, nausea, vomiting, lack of appetite, dehydration, and altered mental status (depression or psychosis) are associated with hypercalcemia. On the electrocardiogram, a shortening of the QT-interval on ECG may draw attention to hypercalcemia.

Concerning bone metabolism, untreated hyperparathyroidism is associated with osteoporosis presented with bone pain, skeletal deformities, and pathological bone fractures. In the past, the very severe form of PHPT associated with severe osteoporosis, bone resorption at multiple sites, bone pains, and cysts was termed Recklinghausen disease (osteitis cystica fibrosa generalisata). So-called brown tumors arising from osteoclasts could be observed on long bones. Nowadays, such severe manifestations of PHPT are very rare.

The commonest renal manifestation of PHPT is renal stones which could be easily recognized by its typical symptoms: back or lumbar pain and hematuria.

How should a patient with asymptomatic PHPT be managed?

When PHPT is proven to be totally symptomless by routine evaluations described above, no specified medical intervention is needed; however, patients should be monitored and followed-up regularly. If one or more results of medical follow-up will meet the criteria of parathyroid surgery, the patients should be referred to an expert surgeon. The recommended medical follow-up approaches for patients with asymptomatic PHPT and indications for surgery are listed in Table 22.2.

Our patient's clinical data met more than one criterion of parathyroid surgery: he was young at the time of the diagnosis (48 years), he had bilateral nephrocalcinosis, moderate hypercalcemia (3.17 mmol/L), and severe hypercalciuria (18 mmol/24 h).

How should a patient with symptomatic PHPT be managed?

In patients who bear symptoms of hypercalcemia or who have sustained renal or skeletal impairment (kidney stones and osteoporosis), surgery is clearly indicated if there are no medical or other contraindications. Localization of pathological parathyroid tissue is essential before parathyroid surgery in order to aide a successful operation.

Which radiological approach is the most sensitive to localize pathological parathyroid tissue?

Neck ultrasound and ^{99m}Technetium-labeled sestamibi scintigraphy/Single photon emission computed tomography (SPECT)-CT are the two primary imaging techniques used for the localization of parathyroid tumors. However, it is often

Table 22.2 Recommended medical follow-up approaches and indications for surgery for patients with asymptomatic PHPT

Investigation	Frequency	Criteria for surgery
Serum calcium	Annually	>0.25 mmol/L (>1.0 mg/dL) above the upper limit of normal
Urinary calcium	Annually	>10 mmol/24 h (>400 mg/24 h)
GFR	Annually	<60 mL/min/1.73 m^2
Three-site bone densitometry with vertebral fracture assessment	Annually	*t*-score < 2.5 at any site, or vertebral fracture
Abdominal imaging	Annually	Presence of nephrocalcinosis or nephrolithiasis
Age at diagnosis		<50 years

very difficult to find the parathyroid adenomas as these are usually rather small. Moreover, the site of the tumor can even be ectopic.

Neck ultrasound of our patient described a 2 cm thyroid nodule without pathological hypervascularization or calcification in the left thyroid gland. No pathological lymph nodes were detected. The lesion was referred as a benign thyroid nodule. A parathyroid tumor was not seen on neck ultrasound.

^{99m}Technetium-labeled sestamibi scintigraphy/SPECT-CT can detect small or ectopic lesions, therefore it is absolutely indicated to perform if the indication of surgery has been established. The ^{99m}Technetium-labeled sestamibi scintigraphy of our patient detected a parathyroid neoplasia behind the left clavicule which was referred as a parathyroid lesion in the ectopic left inferior parathyroid gland. Results of planar scintigraphy and SPECT-CT are shown in Figs. 22.1a and 22.1b, respectively.

What should be done if the parathyroid tumor cannot be localized by neck ultrasound and ^{99m}Technetium-labeled sestamibi scintigraphy/SPECT-CT?

Other imaging techniques like computed tomography and magnetic resonance imaging can be tried, but in patients who did not have neck operations before, direct referral to an expert surgeon can be advised, and the surgeon can usually localize the parathyroid lesion during bilateral neck exploration.

Is it important to assess the dignity of the parathyroid neoplasias detected before surgery?

Yes, because any suspicion of malignancy (palpable neck mass, hypervascularizated neoplasia on ultrasound, and regional lymphadenopathy) should guide the surgeon to be more aggressive during tumor resection. The surgical approach should include resection of any adjacent fibroadipose or muscular soft tissues as well as removal of the ipsilateral thyroid lobe or uninvolved ipsilateral parathyroid glands. Regional lymph node dissection of the central neck nodal compartment may also be required to achieve R0 resection state (microscopically tumor negative margins of the resected tissue).

Is there any method to assess whether the parathyroid tumor resection was complete?

Two laboratory tests could serve as useful tools to estimate surgical success. Significant decrease (>50%) of serum parathyroid hormone concentration *during parathyroid surgery* indicates that the hyperfunctioning parathyroid tissue have been removed successfully. The physiological background of this phenomenon is that half-life of parathyroid hormone in the circulation is quite short (3–5 minutes); therefore confirmation of

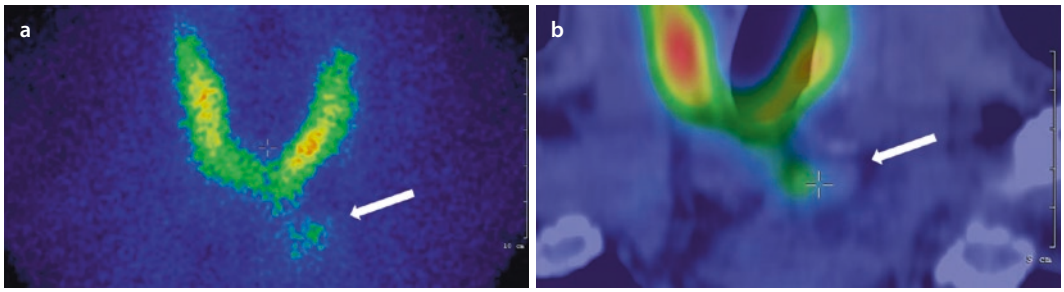


Fig. 22.1 Planar ^{99m}Technetium-labeled sestamibi scintigraphy **a** and SPECT-CT **b** of our patient detected a parathyroid neoplasia in the left inferior parathyroid gland

decreasing serum PTH levels with a rapid assay following removal of the suspected adenoma provides a real-time confirmation of surgical success. *Postoperative* hypocalcemia is also a good sign of the removal of adequate parathyroid gland. Hypercalcemia in primary hyperparathyroidism will cause suppression of parathyroid hormone secretion from the intact, non-tumorous parathyroid glands. After removal of the hyperfunctioning gland, the decreased function of the remaining ones will cause hypocalcemia that is not rarely presented with paresthesias or even tetany. Therefore, serum calcium measurement is mandatory the day after the operation. According to postoperative laboratory results, calcium and vitamin D supplementation may be required. Per definition, cure after parathyroidectomy is defined as normal calcium, phosphate, and parathyroid hormone levels lasting a minimum of 6 months.

The intra- and postoperative laboratory results of our patient are also presented in Table 22.1.

What kinds of further considerations are needed in PHPT diagnosed in a young individual?

According to the recent guidelines, young patients (under the age of 30 years) and all patients with multiple parathyroid tumors should be considered to have genetic testing. The penetrance of PHPT is the highest in multiple endocrine neoplasia type 1 (MEN1). Other familial syndromes in which PHPT could occur include multiple endocrine neoplasia type 2 (MEN2), hyperparathyroidism-jaw tumor syndrome (HPT-JT), and familial isolated hyperparathyroidism (FIHPT).

Surprisingly, the histological report of our patient confirmed that the removed tumor was surrounded by thymus tissue, which was otherwise benign. The in toto removed neoplasia itself was pathologically confirmed as a benign parathyroid adenoma. Genetic testing to screen multiple endocrine neoplasias (MEN1) was done despite he was known to have a single parathyroid adenoma. No mutation was detected with *MEN1* gene sequencing.

How could we differentiate PHPT from secondary and tertiary hyperparathyroidism?

In some cases when patients are presented with bone loss and elevated serum parathyroid hormone levels, secondary and even tertiary causes of PTH hypersecretion should be considered.

The major physiological trigger of PTH secretion is decreased serum ionized calcium concentration. Therefore all pathological conditions which lead to hypocalcemia will consequently cause secondary hyperparathyroidism characterized by low-normal serum calcium and elevated PTH levels. Chronic renal failure, vitamin D deficiency, and diseases with malabsorption are the most common causes of secondary hyperparathyroidism. Furthermore, chronic overstimulation of the parathyroid glands could result in parathyroid nodular hyperplasia with autonomous secretion of PTH. This condition is termed tertiary hyperparathyroidism and it is mostly observed in chronic renal failure, in most patients on chronic hemodialysis. The affected patients will exhibit unresponsiveness to medical therapy of secondary hyperparathyroidism, therefore hypercalcemia and elevated PTH levels will be measured despite cessation of vitamin D supplementation.

Are there medical therapies available for patients who refuse or are ineligible for surgery?

Bisphosphonates can be given to patients with osteoporosis. Cinacalcet, a molecule activating the calcium-sensing receptor can decrease the secretion of PTH and thereby can be an efficient treatment modality,

however, it is mainly given to patients with secondary or tertiary hyperparathyroidism on chronic hemodialysis.

Can vitamin D be given to patients with primary hyperparathyroidism?

Patients with PHPT have usually subnormal vitamin D (25-OH-vitamin D) levels. After a successful operation, deficiency in vitamin D could lead to prolonged and severe hypocalcemia. Low doses of vitamin D (e.g., 600–1000 IU/day) can be given to patients without severe hypercalcemia, but careful and regular monitoring of serum and urinary calcium parameters is required.

How frequent is parathyroid carcinoma and when should it be suspected?

Malignant tumors of parathyroid glands are representing less than 1% of all parathyroid neoplasias. The disorder is usually sporadic, however, a few genetic syndromes may include parathyroid carcinoma (e.g., hyperparathyroidism-jaw tumor syndrome). The signs and symptoms are very similar to those of PHPT; therefore, it could be challenging to predict the malignancy of a parathyroid tumor in the preoperative settings. On ultrasound, the enlarged tumor size, hypervascularization, and regional lymphadenopathy may reflect the malignant behavior of a parathyroid neoplasia. The preoperative diagnosis or at least establishing a strong suspicion is critical as surgical resection of the tumor should be more extended in parathyroid carcinomas.

Tips

The reader is advised to read the chapter on multiple endocrine neoplasia type 1 (▶ Chap. 50) and humoral hypercalcemia of malignancy (▶ Chap. 49). The treatment of hypercalcemia is presented in the chapter on Humoral hypercalcemia of malignancy.

Take Home Messages

- Primary hyperparathyroidism is a common cause of parathyroid hormone-dependent hypercalcemia.
- Due to the widely used serum calcium measurement in routine laboratory testing, the vast majority of patients is diagnosed as an asymptomatic PHPT.
- Establishing the diagnosis of PHPT is based only on laboratory measurements.
- All patients should be screened for target organ involvement of PTH action. Therefore, three-site bone densitometry and renal imaging should be performed after getting the diagnosis of PHPT.
- All asymptomatic patients who met the criteria for parathyroid surgery and all patients with symptoms of bone and kidney failure or signs of hypercalcemia should be referred to an expert surgeon.
- Surgical cure could be easily proven by detecting intraoperative serum PTH decline and postoperative hypocalcemia.
- Young patients (<30 years) and those who have multiple parathyroid neoplasias should be suggested to have genetic testing for MEN1 syndrome.

Suggested Reading

1. Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C, Potts JT Jr. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol Metab. 2014;99:3561–9. https://doi.org/10.1210/jc.2014-1413.
2. Fingeret AL. Contemporary evaluation and management of parathyroid carcinoma. JCO Oncol Pract. 2020; epub ahead print. https://doi.org/10.1200/jop.19.00540.
3. Lassen T, Friis-Hansen L, Rasmussen AK, Knigge U, Feldt-Rasmussen U. Primary hyperparathyroidism in young people. When should we perform genetic testing for multiple endocrine neoplasia 1 (MEN-1)? J Clin Endocrinol Metabol. 2014;99:3983–7. https://doi.org/10.1210/jc.2013-4491.
4. Saponaro F, Cetani F, Mazoni L, Apicella M, Di Giulio M, Carlucci F, Scalese M, Pardi E, Borsari S,

Bilezikian JP, Marcocci C. Hypercalciuria: its value as a predictive risk factor for nephrolithiasis in asymptomatic primary hyperparathyroidism? J Endocrinol Invest. 2020;43:677–82. https://doi.org/10.1007/s40618-019-01162-y.
5. Silva BC, Cusano NE, Bilezikian JP. Primary hyperparathyroidism. Best Pract Res Clin Endocrinol Metab. 2018;32:593–607. https://doi.org/10.1016/j.beem.2018.09.004.
6. Toke J, Patócs A, Balogh K, Gergics P, Stenczer B, Rácz K, Tóth M. Parathyroid hormone-dependent hypercalcemia. Wien Klin Wochenschr. 2009;121:236–45. https://doi.org/10.1007/s00508-009-1149-z.

Hypoparathyroidism

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Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_23

23

Opening

The clinical features, diagnosis, and treatment of hypoparathyroidism will be reviewed in this chapter. Hypoparathyroidism is an uncommon disorder. The typical laboratory findings of primary hypoparathyroidism include hypocalcemia and hyperphosphatemia in the presence of abnormally low or undetectable levels of parathyroid hormone (PTH).

The symptoms of hypoparathyroidism are quite diverse and related to the low levels of calcium in the blood. The severity of the condition ranges from mild symptoms such as numbness in the fingers, toes, or around the lips to severe muscle cramps and muscle spasms (tetany).

Definition of the Disease

Hypoparathyroidism is a rare disorder caused by parathyroid hormone deficiency. Hypoparathyroidism affects females and males in equal numbers.

The causes of hypoparathyroidism include the abnormal development, or the destruction of the parathyroid glands (e.g., during thyroid surgery or by an autoimmune process), the impairment of PTH action or the altered regulation of PTH production (◘ Table 23.1). The prevalence of hypoparathyroidism is estimated between 23 and 37/100,000. The most common cause of acquired hypoparathyroidism is neck surgery that is responsible for about 75% of cases. The second most common acquired cause in adults is thought to be autoimmune disease that is either limited to the parathyroid glands or forms part of a disease involving multiple endocrine glands (e.g., more than, 80% of autoimmune polyendocrine syndrome type 1 patients have hypoparathyroidism). In this case, hypoparathyroidism can be a result of autoimmune destruction of the parathyroid glands. In addition, autoantibodies that stimulate calcium-sensing receptor (CaSR) activity, even when blood calcium levels are lower than normal, can cause the inhibition of PTH secretion from the parathyroid. Such CaSR-activating autoantibodies have been identified in patients with idiopathic hypoparathyroidism and autoimmune polyendocrine syndrome type 1 (APS-1). In APS-1, common autoantibody targets include parathyroid-expressed NACHT leucine-rich-repeat protein 5 (NALP5) and cytokines. Treatment with an immunotherapy regimen against immune checkpoint inhibitors resulted in a rare case of immune-mediated hypoparathyroidism. Remaining cases of acquired hypoparathyroidism are due to a variety of infiltrative disorders in which the parathyroid glands are affected by iron or copper overload or metastatic disease. Genetic disorders are rare causes of hypoparathyroidism that are most often identified in childhood (◘ Table 23.1). From the hereditary causes DiGeorge syndrome (type 1) should be highlighted that is a complex developmental abnormality caused by a deletion on chromosome 22. The triad of parathyroid, thymus hypoplasia (T-cell deficiency), and heart development abnormalities constitute DiGeorge syndrome.

The clinical characteristics of hypoparathyroidism are mainly related to hypocalcemia. The severity of symptoms depends on the duration and intensity of hypocalcemia. Hypoparathyroidism is characterized by many, diverse symptoms and signs; however, the main manifestation is the direct consequence of increased excitability of muscles and nerves caused by decreased blood calcium levels. Patients most often present with paresthesias, cramps, or tetany. However, the disorder could also manifest itself as an acute (sometimes life-threatening) disorder leading to laryngospasm, bronchospasm, seizures or cardiac rhythm disturbances, prolonged corrected QT (QTc) interval, or T wave abnormalities. Long-term hypoparathyroidism is often associated with calcification of the basal ganglia (Fahr disease) and cataracts. In chronic cases of hypocalcemia, symptoms become less specific, ranging from asymptomatic states to atypical clinical presentations, such as neuropsychiatric manifestations (mood disorders and depression).

Table 23.1 Causes of hypoparathyroidism

	Inheritance	Causative gene (if hereditary)
Parathyroid gland destruction or damage		
Post-surgical hypoparathyroidism (thyroidectomy, parathyroidectomy, and radical neck dissection)	–	
Radiation-induced destruction of parathyroid glands	–	
Autoimmune hypoparathyroidism	–	
Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (APECED, APS-1 syndrome)	AR	*AIRE*
Infiltrative diseases:		
Iron overload (hemochromatosis)	AR[a]	*HFE* and others
Copper overload (Wilson disease)	AR	*ATP7B*
Metastatic disease	–	
Checkpoint inhibitors therapy	–	
Disorders of parathyroid hormone secretion		
PTH gene mutations	AD or AR	*PTH*
Autosomal dominant hypocalcemia type 1	AD	*CaSR*
Autosomal dominant hypocalcemia type 2	AD	*GNA11*
Neonatal hypoparathyroidism due to maternal hypercalcemia	–	
Hypo- or hypermagnesemia	–	
Disorders of parathyroid gland formation		
Familial isolated hypoparathyroidism	AD or AR	*GCM2* *PTH*
X-Linked hypoparathyroidism	XR	*SOX3*
DiGeorge syndrome type 1 (22q11.2 deletion syndrome)	AD	*TBX1*
DiGeorge syndrome type 2	AD	*NEBL*
CHARGE syndrome	AD	*CHD7* *SEMA3E*
Sanjad-Sakati syndrome[a]	AR	*TBCE*
Kenny-Caffey syndrome type 1[b]	AR	*TBCE*
Kenny-Caffey syndrome type 2[b]	AD	*FAM111A*

(continued)

Table 23.1 (continued)

	Inheritance	Causative gene (if hereditary)
Hypoparathyroidism, deafness, and renal (HDR) syndrome	AD	*GATA3*
Mitochondrial diseases LCHAD MTP Pearson marrow-pancreas syndrome MELAS Kearns-Sayre syndrome	AR	*HADHA* mtDNA mtDNA mtDNA

[a]Hereditary hemochromatosis is mostly inherited as an autosomal recessive trait, but mutations in some genes (e.g., ferroportin) are inherited in an autosomal dominant manner

[b]These rare hereditary syndromes are associated with short stature and bone dysplasia

AD autosomal dominant, *AR* autosomal recessive, *XR* X-linked recessive, *PTH* parathyroid hormone, *CaSR* calcium-sensing receptor, *CHARGE* Coloboma, Heart defects, choanal Atresia, Retarded growth, Genital hypoplasia, Ear anomalies/deafness, LCHAD long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency, *MELAS* mitochondrial encephalopathy, lactic acidosis, and Stroke-like episodes syndrome, *mt* mitochondrial, *DNA* deoxyribonucleic acid, *MTP* Mitochondrial trifunctional protein

Case Presentation

A previously healthy 42-year-old man consulted his primary care physician because of progressive numbness of the face and the hands, but no cause was identified. He also experienced fatigue, loss of concentration, and decreased interest in most activities in the previous 6 months. Past medical and family history was unremarkable. He reported no history of tobacco or alcohol use. His physical examination was normal. No objective motor or sensory deficit was found, and the classical Chvostek's sign was absent.

Blood results indicated hypocalcemia and hyperphosphatemia associated with a low parathyroid hormone level (Table 23.2). His serum levels of albumin, 25-hydroxyvitamin D (25-OH-D), magnesium, as well as the results of liver and kidney function tests, were in the normal ranges. Based on these findings, hypoparathyroidism was diagnosed.

Table 23.2 Laboratory findings of the patient

Blood parameter	Result	Normal range
Calcium	1.9 mmol/l 7.62 mg/dL	2.2–2.65 mmol/l 8.6–10.2 mg/dL
Phosphate	1.79 mmol/l 5.54 mg/dL	0.81– 1.45 mmol/l 3.0–4.5 mg/dL
Magnesium	0.98 mmol/l 2.38 mg/dL	0.77– 1.03 mmol/l 1.6–2.6 mg/dL
PTH	2.0 pg/mL 0.21 pmol/L	10–85 pg/mL 1.6–6.9 pmol/L

How is hypoparathyroidism diagnosed?

The diagnosis should be established on the measurement of albumin-corrected or ionized serum calcium that are below the lower limits of the normal range and low or undetectable levels of PTH. If the clinical situation warrants, the chemistry panel should include phosphate and magnesium, 25-hydroxyvitamin D, 24-hour urinary calcium excretion, estimated or calculated glomerular filtration rate (GFR).

What are the classical Chvostek's and Trousseau's signs?

Chvostek's sign is elicited by tapping the skin over the facial nerve anterior to the external auditory meatus. Ipsilateral contraction of the facial muscles occurs in individuals with hypocalcemia. A positive Chvostek sign is seen in 10–20% of healthy people.

Trousseau's sign is a carpopedal provoked by inflating the blood pressure cuff to a level above the systolic pressure for 3 minutes. Carpal spasm presents as flexion of the wrist and of the metacarpal phalangeal joints, extension of the interphalangeal joints, and adduction of the thumb. Trousseau sign occurs in approximately 1–4% of normal subjects. (The Trousseau's sign can be dangerous to provoke, and it is therefore not recommended nowadays.)

When should we consider a genetic problem in the background of symptoms?

Genetic disorders typically become apparent in childhood. Monogenic abnormalities and chromosomal microdeletions represent the major cause of hypoparathyroidism in children. Genetic forms of hypoparathyroidism mostly occur as a component of syndromic disorders (Table 23.1).

Is a germ-line mutation testing warranted?

If the patient's presentation suggests a genetic basis (e.g., young age, family history, and multiple autoimmune features), germ-line mutation testing and genetic counseling should be considered.

How should the patient be treated?

Treatment of hypoparathyroidism is aimed at reducing symptoms, correcting hypocalcemia and hyperphosphatemia without causing abnormally high levels of calcium in the blood or in the urine. To avoid long-term side effects, the goal of treatment is to maintain blood calcium levels near the lower end of the normal range while preventing symptoms of hypocalcemia.

Actual treatment depends on the severity of presenting symptoms and the rate of development of hypocalcemia. Notably, in asymptomatic patients with an acute decrease in serum corrected calcium levels to lower than 1.9 mmol/L (≤7.5 mg/dL), serious complications may develop if left untreated.

How to treat acute hypoparathyroidism?

Acute hypocalcemia requires emergency management. The presence of seizures, tetany, laryngospasm, or bronchospasm signals a life-threatening condition that necessitates the infusion of 10% calcium gluconate (approximately 90 mg of elemental calcium per 10 ml of solution) over a period of 10–20 minutes, often followed by a continuous infusion to prevent recurrent hypocalcemia while oral therapy could be initiated. Calcium gluconate is the preferred drug as it can be administered via a peripheral vein. Calcium gluconate causes less tissue necrosis in case of extravasation than calcium chloride, although ECG monitoring is recommended during calcium infusions.

How to treat chronic hypoparathyroidism?

Chronic hypoparathyroidism is treated with oral supplementation of calcium and vitamin D (activated forms: calcitriol and alfacalcidol or inactivated forms: cholecalciferol or ergocalciferol). This treatment can be supplemented with thiazide diuretics, oral magnesium supplementation, phosphate binders, and dietary restriction of phosphates and sodium.

Calcium supplementation

The usual amount of calcium is around 1–2 g per day, split into two or more doses. It should be noted that the intestinal absorption of calcium is saturated at 500 mg; therefore, higher amounts per

dose should not be prescribed, as it is unlikely to be beneficial.

- The most commonly used calcium salts are carbonate and citrate. Calcium carbonate (which contains 40% elemental calcium) is the less expensive preparation; however, it requires an acidic environment for optimal absorption. In cases of achlorhydria (i.e., after gastrectomy) or low acidity (i.e., use of proton pump inhibitors), calcium citrate is preferred despite a lower content of elemental calcium (20%) and a higher cost.

- *Vitamin D*

- As the production of 1,25-dihydroxyvitamin is reduced in hypoparathyroidism, the generally preferred treatment of hypoparathyroidism is calcitriol. Calcitriol is preferred (over non-activated ergocalciferol or cholecalciferol) because of its potency, rapid onset of action, and shorter half-life, making it more suitable for chronic treatment. Usually the daily dosage of calcitriol ranges from 0.5 to 2 μg per day.

- Alfacalcidol (1α-hydroxyvitamin D) is a vitamin D analogue that is rapidly activated in the liver to 1,25-dihydroxyvitamin D. The usual daily dosage of alfacalcidol ranges from 0.5 to 3.0 μg.

- Another alternative for vitamin D supplementation is the use of vitamin D precursors (ergocalciferol or cholecalciferol). Vitamin D precursors have often been used in the past when access to calcitriol/alfacalcidol was restricted.

- High doses of vitamin D may are needed to treat hypoparathyroidism (Table 23.3); however, high doses of vitamin D may have unwanted actions at the systemic level. Thus, the currently recommended vitamin D supplementation is restricted to a daily dose of 400–800 IU to patients already treated with activated vitamin D analogues, in order to ensure an adequate vitamin D status. This daily cholecalciferol dose will most likely ensure a serum 25-hydroxyvitamin D (25-OH-D) level above 50 nmol/l (>20ng/ml).

Table 23.3 Vitamin D metabolites in the management of chronic hypoparathyroidism

Medication	Typical dose
Calcitriol (1,25(OH)2D3)	0.25–2.0 μg once or twice daily
Alfacalcidol (1α-hydroxyvitamin D)	0.5–4 μg once daily
Ergocalciferol or cholecalciferol	25,000–200,000 IU daily

- *Thiazide diuretics*

- Thiazide diuretics can be used to prevent and reduce hypercalciuria caused by calcium and vitamin D therapy. Once the 24-hour urinary calcium level approaches 250 mg, a thiazide diuretic can be added. The hypocalciuric effect of thiazide diuretic is dose-dependent, and treatment should preferably be combined with sodium restriction.

- *Dietary recommendations limiting hyperphosphatemia*

- Hyperphosphatemia may be addressed by minimizing the dietary intake of phosphate and, if needed, with the addition of phosphate binders to control or prevent an unacceptable calcium–phosphate product.

- *Magnesium supplementation*

- Magnesium plays an important role in calcium homeostasis. Magnesium is known to modulate the function of the parathyroid glands. Therefore, persistent hypomagnesemia must be corrected (250–1000 mg of elemental magnesium divided into 2–4 doses per day).

What can be done if conventional treatment is not effective?

PTH replacement has been approved for the treatment of hypoparathyroidism in adults who have disease refractory to conventional therapy. Many studies have shown that hypocalcemia can be adequately managed in most patients by once- or twice-daily subcutaneous injections of the amino-terminal fragment of PTH known as teriparatide (PTH (1–34)) or recombinant human PTH (1–84) (rhPTH).

How should the treatment of chronic hypoparathyroidism be monitored?

In cases of permanent, chronic hypoparathyroidism, regular monitoring is mandatory. Routine biochemical monitoring, as well as assessment of symptoms of hypocalcemia and hypercalcemia are recommended at regular time intervals.

Laboratory testing includes serum measurements of calcium, phosphate, magnesium, blood urea nitrogen/creatinine, and estimated glomerular filtration rate (eGFR) every 3–6 months. This should be accompanied by measurements of serum 25-OH-D as well as 24-hour urine calcium and creatinine every 6–12 months.

In case of changes in therapy, more frequent biochemical monitoring is required weekly or every other week.

In the case of nephrolithiasis or nephrocalcinosis renal ultrasound is indicated at the initial evaluation and every 1–5 years afterward.

Annual measurement of bone mineral density is recommended using dual energy X-ray absorptiometry (DXA) for patients under treatment with rhPTH (PTH 1–84) or teriparatide (PTH 1–34 fragment), while for patients receiving conventional treatment, osteoporosis guidelines should be followed.

The follow-up for potential soft tissue calcification requires an annual ophthalmologic examination, and, in the case of clinical suspicion, a brain CT scan for the detection of calcifications in the basal ganglia.

What are treatment options and what are the treatment targets for serum calcium in pregnancy?

Calcium supplements are safe in pregnancy, as is the use of calcitriol and cholecalciferol. The use of thiazide diuretics is not recommended during pregnancy. The safety of replacement therapy with PTH (1–84) and PTH (1–34) has not been evaluated during pregnancy.

In pregnancy, serum calcium level is maintained in the low-normal reference range.

Serum calcium concentrations should be measured frequently during pregnancy and lactation in women with hypoparathyroidism. This should be evaluated every 3–4 weeks throughout pregnancy. During lactation, monitoring should occur every 4–6 weeks to ensure stability of maternal calcium levels. If changes in the dose of calcium supplementation or calcitriol/cholecalciferol are recommended, repeat the serum calcium in 1–2 weeks. Maintain the 24-hour urinary calcium excretion and 25-hydroxyvitamin D in the normal reference range.

What is pseudohypoparathyroidism?

Pseudohypoparathyroidism is a rare, hereditary disorder characterized by peripheral resistance (inadequate response) to parathyroid hormone. It was

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described for the first time by Fuller Albright and colleagues in 1942. The exact prevalence of pseudohypoparathyroidism is unknown, but its prevalence is estimated at approximately 0.79 per 100.000. Pseudohypoparathyroidism affects more females than males. The primary causes of pseudohypoparathyroidism are genetic or epigenetic mutations in the *GNAS* gene. (The *GNAS* gene codes for an alpha subunit of the guanine nucleotide-binding protein and is thus involved in the signal transduction of G-proteins.)

- Its onset usually occurs during childhood with clinical manifestations of hypocalcemia and laboratory studies that reveal hypocalcemia, hyperphosphatemia, and elevated serum PTH concentrations with normal renal function. 25-hydroxyvitamin D and magnesium levels are normal.

- Some forms of the disease are associated with a characteristic skeletal phenotype of shortened bones in the feet and hands (brachymetacarpals, brachymetatarsals—mostly the fourth fingers are affected), short neck, short stature, abnormally round face, obesity, dental hypoplasia (Albright hereditary osteodystrophy, pseudohypoparathyroidism type 1a). Headaches, weakness, lethargy, and cataracts may also be present. In pseudopseudohypoparathyroidism (caused by *GNAS* mutations of the paternal allele), the characteristic phenotypic features of Albright hereditary osteodystrophy are present without PTH resistance.

- The mainstay of treatment for patients with permanent active vitamin D supplementation with or without calcium. Calcitriol 0.25–1.0 μg per day should be used. Calcium carbonate or calcium citrate should be given in the form of 2–8 g elemental calcium daily in divided doses to keep calcium at the low end of normal. PTH levels require monitoring during treatment and maintain serum PTH levels in the mid to upper normal range if possible.

Tips

The reader is advised to read the preceding chapter on primary hyperparathyroidism (▶ Chap. 22), and the chapter on Addison's disease and autoimmune polyendocrine syndrome type 2 (▶ Chap. 31), where the autoimmune polyendocrine syndrome type 1 is also discussed shortly.

Take Home Messages

- The major hallmark of hypoparathyroidism (a relatively rare disease) is hypocalcemia. Its symptoms are consequences of hypocalcemia, such as paresthesias, muscle cramps, seizures, and laryngospasm.
- Other manifestations of hypoparathyroidism include such divergent symptoms as calcification of the basal ganglia, cataracts, and neuropsychiatric disorders.
- Hypoparathyroidism is most frequently associated with operations on the anterior neck that may result in injury or removal of the parathyroid gland. Other rare genetic or autoimmune causes may be limited to the parathyroid gland or be part of a multiglandular syndrome.
- The treatment aims to reach and maintain serum calcium levels within the normal range, potentially in its lower part, thus preventing symptoms of hypocalcemia and minimize side effects of its usual treatment with oral calcium and active vitamin D (calcitriol or alfacalcidol). A more novel way of treatment is subcutaneous parathyroid hormone therapy.
- Even adequate treatment frequently causes hypercalciuria, nephrocalcinosis, nephrolithiasis, and renal insufficiency, and thus careful and regular monitoring is a necessity to decrease the potential long-term harms of treatment also an important aim of the development of novel therapies.

Suggested Reading

1. Brandi ML, Bilezikian JP, Shoback D, Bouillon R, Clarke BL, Thakker RV, Khan AA, Potts JT Jr. Management of hypoparathyroidism: summary statement and guidelines. J Clin Endocrinol Metab. 2016;101(6):2273–83. https://doi.org/10.1210/jc.2015-3907.
2. Clarke BL, Brown EM, Collins MT, Jüppner H, Lakatos P, Levine MA, Mannstadt MM, Bilezikian JP, Romanischen AF, Thakker RV. Epidemiology and diagnosis of hypoparathyroidism. J Clin Endocrinol Metab. 2016;101(6):2284–99. https://doi.org/10.1210/jc.2015-3908.
3. Gafni RI, Collins MT. Hypoparathyroidism. N Engl J Med. 2019;380:1738–47. https://doi.org/10.1056/NEJMcp1800213.
4. Khan AA, Koch CA, Van Uum S, Baillargeon JP, Bollerslev J, Brandi ML, Marcocci C, Rejnmark L, Rizzoli R, Shrayyef MZ, Thakker R, Yildiz BO, Clarke B. Standards of care for hypoparathyroidism in adults: a Canadian and International Consensus. Eur J Endocrinol. 2019;180:P1–P23. https://doi.org/10.1530/EJE-18-0609.
5. Khan AA, Clarke B, Rejnmark L, Brandi ML. Hypoparathyroidism in pregnancy: review and evidence-based recommendations for management. Eur J Endocrinol. 2019;180:R37–44. https://doi.org/10.1530/EJE-18-0541.
6. Mannstadt M, Bilezikian JP, Rajesh V, Thakker RV, Hannan FM, Clarke BL, Rejnmark L, Mitchell DM, Vokes TJ, Winer KK, Shoback DM. Hypoparathyroidism. Nat Rev Dis Primers. 2017;31(3):17055. https://doi.org/10.1038/nrdp.2017.55.
7. Mantovani G, Bastepe M, Monk D, de Sanctis L, Thiele S, Usardi A, Ahmed SF, Bufo R, Choplin T, De Filippo G, Devernois G, Eggermann T, Elli FM, Freson K, García Ramirez A, Germain-Lee EL, Groussin L, Hamdy N, Hanna P, Hiort O, Jüppner H, Kamenický P, Knight N, Kottler ML, Le Norcy E, Lecumberri B, Levine MA, Mäkitie O, Martin R, Martos-Moreno GÁ, Minagawa M, Murray P, Pereda A, Pignolo R, Rejnmark L, Rodado R, Rothenbuhler A, Saraff V, Shoemaker AH, Shore EM, Silve C, Turan S, Woods P, Zillikens MC, Perez de Nanclares G, Linglart A. Diagnosis and management of pseudohypoparathyroidism and related disorders: first international consensus statement. Nat Rev Endocrinol. 2018;14(8):476–500. https://doi.org/10.1038/s41574-018-0042-0.

Osteoporosis

Csaba Horvath

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_24

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Opening

Osteoporosis is a metabolic bone disease characterized by progressive loss of bone mass and qualitative changes in microarchitecture, resulting in high prevalence of fragility fractures. The disease is most common in older ladies, but older men and younger people with some chronic diseases or medications are also involved. Osteoporosis yearly causes more than nine million fractures in the world, followed by enormous medical and social costs, higher mortality, and decreased quality of life. However, established methods for diagnosis and treatment have been developed in the last decades, ensuring good chance for fracture prevention.

Definition of the Disease

The healthy bone gets over a continuous renewal called bone remodeling through the whole adult life. This process occurs mainly on inner and outer bone surfaces, starting with local bone resorption made by osteoclasts and continuing in local formation of an *equal amount* of new bone produced by osteoblasts. The process goes under a strict local control by osteocytes ensuring mechanical competence of bone, but local and systemic humoral controls also impact by targeting the stability of extracellular calcium concentration. The main regulators of remodeling are the mechanical loading, estrogens, and parathyroid hormone (PTH), however, many more regulatory systems (including other hormones, inflammatory cytokines, sympathetic nervous system, etc.) exert as modulators. Further conditions of the normal remodeling are the normal availability of calcium, protein, energy, and calcitriol to the bone tissue, along with normal circulation.

Osteoporosis is a disease characterized by higher and unbalanced remodeling: increased bone resorption is followed by less increased or normal or even decreased bone formation, resulting in net loss of bone mass in every remodeling sites. High and unbalanced remodeling can come from decreased loading (osteocytes decrease the amount of unused bone), from menopause or hypogonadism (osteoclasts get out of inhibitory effects of estrogens), from excess PTH effect (preventing hypocalcemia of any origin, including insufficient availability of calcium and/or calcitriol to bone). Effects suppressing bone formation (e.g., high glucocorticoid level) also cause imbalance and consequent bone loss. Moreover, while the mechanical competence of the healthy bone is based not only on sufficient bone mass but also on the expedient microarchitecture, unfortunately the increased remodeling removes tissue from every bone sites regardless of the microstructure. Thereby, the microstructural damage is added to the bone loss resulting in fragility.

In consequence—and independently of the origin of osteoporosis—the pathologic process decreases the amount and deteriorates the microarchitecture of bone. The weakened bones can break from low level of impact that would not normally break a healthy bone. The low-trauma fracture embodies the clinical presentation of osteoporosis and burdens the patient and the society with pain, decreased life quality, disability, mortality, and high costs. Therefore, the management of osteoporosis targets to find patients with osteoporosis *and* high fracture risk, followed by approaches strengthening bones and preventing subsequent fractures.

Case Presentation

A 63-year-old woman was referred to our endocrine and metabolic bone service because of two rib fractures having occurred in last year due to two small traumatic events. She had two children and her menstrual cycle ended 12 years ago. At the age of 30 years, she had Graves' disease treated with thiamazole for 18 months. She is treated for mild hypertension (perindopril). In addition, she takes 3000 IU vitamin D3 and 1000 mg calcium carbonate every day and regularly consumes dairy products. Her first bone fracture occurred 6 years ago at the left wrist after a fall at home. Three years ago she uplifted her grandson—since then, a low back pain presented frequently, and this was her only complaint. Her body weight: 61 kg, height: 162 cm (decreased by 4 cm). Physical examination showed increased kyphosis and shortening of the spine, horizontal skin-folds on the back, and only a 2 cm distance between the lowest rib and the top of hip bone.

Is this case history typical for osteoporosis?

This is a very representative osteoporotic story. The older age and female sex are the strongest risk factors for developing osteoporosis. Menopause is also a strong risk factor and our patient was living in her second decade with estrogen deficiency. The former hyperthyroidism increased bone resorption and decreased bone mass during its active period, however, the recovery of the thyroid could not guarantee the complete restoration of bone, particularly because of microarchitectural destructions. Beyond these risk factors, she suffered three fractures due to small traumas: this is the most characteristic feature of advanced osteoporosis.

What bone fractures are typical for osteoporosis?

Fractures at the wrist, hip, and vertebrae are the most common sites of osteoporotic fractures. However, after the age of 50 years, most sites of fractures are considered characteristic of osteoporosis, like humerus, ribs, tibia, pelvis, and femoral but not the ankle and skull. Our patient had forearm and rib fractures. It is important to clear if vertebral fractures have also occurred because of chronic low back pain and physical alterations of the spine. The vast majority of vertebral fractures are silent, being discovered as incidental findings by X-ray done for other reason. Magnetic resonance imaging (MRI) is the best method for targeted search of vertebral fractures; however, a lateral X-ray of spine can also be helpful if analyzed by an expert radiologist. Recently, bone densitometry provides a new, quick, cheap, and safe technic (vertebral morphometry) to detect compressed vertebrae. Figure 24.1a shows a grade-1 fracture of the 11. thoracic vertebra while Fig. 24.1b shows severe multiple deformities on vertebral morphometry.

This patient was barely free of symptoms except for a chronic back pain sometimes. Can we call osteoporosis a silent disease?

Absolutely, but it is more precise to call it a "silent killer." Bone loss and structural damage goes without pain through years or decades, and the patient doesn't know about her illness. Osteoporosis makes symptoms only when bones break, surprisingly due to a simple fall or small trauma that previously has not been dangerous. Unfortunately, at time of the first fracture, the bone is seriously ill and we are long after the chance of early diagnosis. Considering that reversible bone loss goes hand in hand with the irreversible microarchitectural deterioration, occurrence of low-trauma fractures suggest advanced osteoporosis. Particularly the hip and spine

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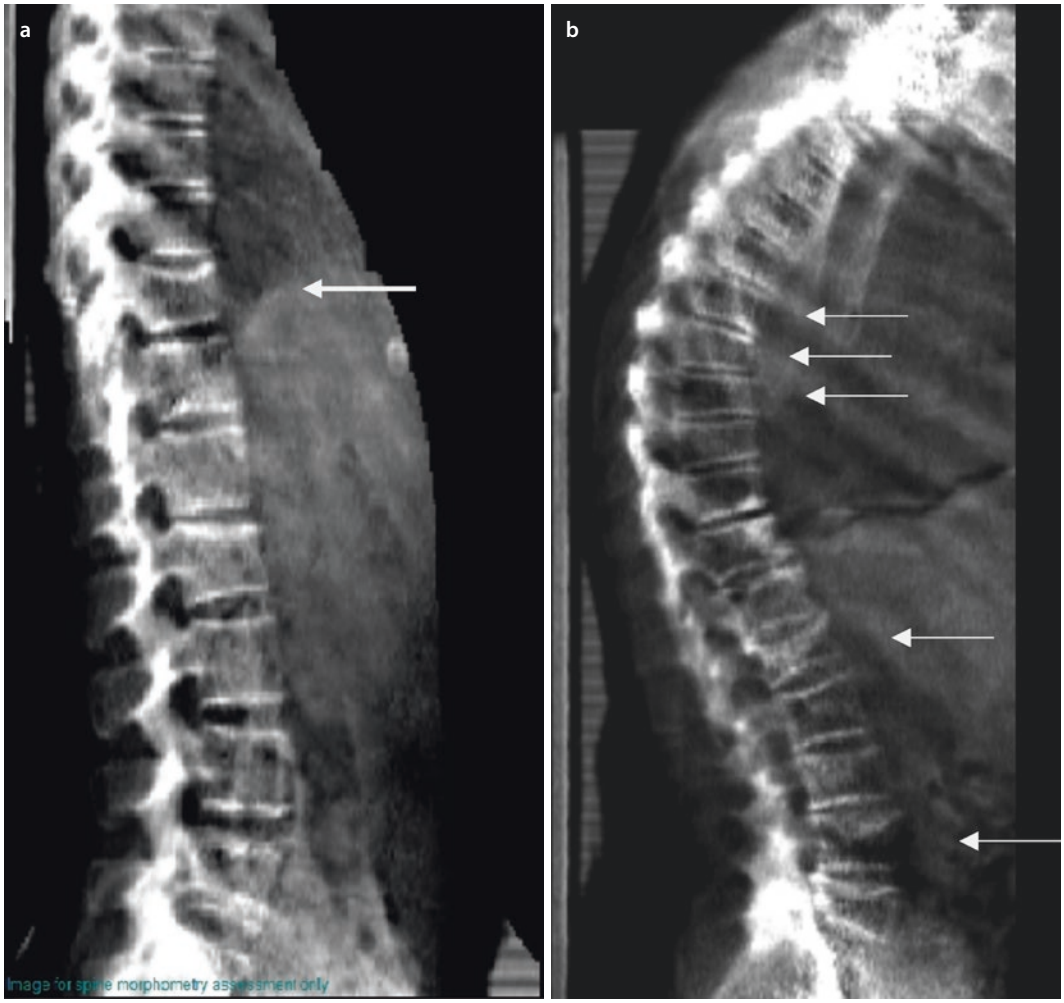

Fig. 24.1 **a** Minor (grade-1) deformity of the 11. thoracic vertebra. **b** Severe and multiple vertebral deformities (wedge, biconcavity, and crush) of thoracic and lumbar spine (arrows)

fractures can result in disability, poor quality of life, and increased mortality of any reason.

How shall we diagnose the suspected osteoporosis?

Bone densitometry (dual-energy X-ray absorptiometry, DEXA) is worldwide the basic method to identify osteoporosis. Absorption of X-ray photons passing through bone depends on the mineral content of that tissue, so measurement of absorption gives an accurate information about mineral mass of bone (BMD, bone mineral density, g/cm^2). BMD is higher in men and in young adults, then decreases by age. The operational definition of osteoporosis is based on the *T*-score that means the difference of a measured BMD and the young female adult mean BMD, expressed in standard deviations of reference database (Table 24.1). For patients younger than 40 years, a comparison of BMD to the mean of age- and sex-matched reference BMD is used, termed *Z*-score (normal: from −2.0 to +2.0).

For clinical purposes, BMD used to be measured at lumbar spine, femoral neck (or total hip), and forearm (distal third of radius). Scientific definition of osteoporosis

Table 24.1 Classification of bone densitometry results in *T*-scores

T	> −1.0	Healthy bone
	Between −1.0 and −2.5	Osteopenia (low bone mass)
	≤ −2.5	Osteoporosis (metabolic bone disease)
	< −2.5 plus fractures	Established osteoporosis

is based on the hip *T*-score below −2.5, while in clinical practice a wide international consensus suggests to scan all three bones and accept the lowest *T*-score of any bone for the diagnosis (Fig. 24.2).

Osteopenia is low bone mass (*T*-score between −1.0 and −2.5) but not identical to osteoporosis as a disease. On the other hand, osteopenia also increases fracture risk and can progress to osteoporosis.

Let's see the bone densities of this patient!

Table 24.2 summarizes the measured BMDs and the calculated scores. Note the differences of *T*-scores at different bones: osteoporosis is not uniform in every bone, big differences can be seen at different sites, depending on genetics, lifestyle, and physical activity. The lowest *T*-score makes the diagnosis—in this case this is the spine, and the diagnosis for the patient is osteoporosis.

Never do diagnosis from separated interpretation of one bone! A wrong example would be to say: "this patient has a spinal osteoporosis but only osteopenia at the peripheral bones." Forget it! If any *T*-score is below −2.5 then it is osteoporosis—seen from densitometry.

The lowest T-score of this patient is −3.2. Is it equivalent with clinical diagnosis of postmenopausal osteoporosis?

Certainly not, as other metabolic bone diseases and secondary forms of osteoporosis also decrease bone mass. Bone densitometry alone detects only calcipenic osteopathy—a collecting name of diseases accompanied by low bone mass but with need of different therapies. Hence, the next step of the diagnostic procedure is to differentiate among potential reasons—consuming data of medical history, physical examination, and laboratory tests. ▶ Box 24.1 surveys such diseases of practical importance.

Box 24.1 Common Diseases Associated with Osteoporosis (Secondary Osteoporosis) ***(the most importants are in italics)***

- **Endocrine:** *glucocorticoid-induced osteoporosis, hyperthyroidism, hypogonadism, hyperparathyroidism,* acromegaly, growth hormone deficiency, *diabetes mellitus type-1 and -2*
- **Hematological:** *multiple myeloma* and monoclonal gammopathies
- **Gastrointestinal/Nutritional:** *celiac disease*, chronic liver diseases, inflammatory bowel disease, and gastric bypass surgery
- **Renal:** *chronic kidney disease, renal hypercalciuria*, and tubular acidosis
- **Pulmonary:** *chronic obstructive pulmonary disease (COPD)*
- **Autoimmune:** *rheumatoid arthritis* and systemic lupus erythematosus
- **Drug-induced:** *aromatase-inhibit*ors (breast cancer), loop diuretics, *antiandrogens* (prostate cancer), and protonpump inhibitors

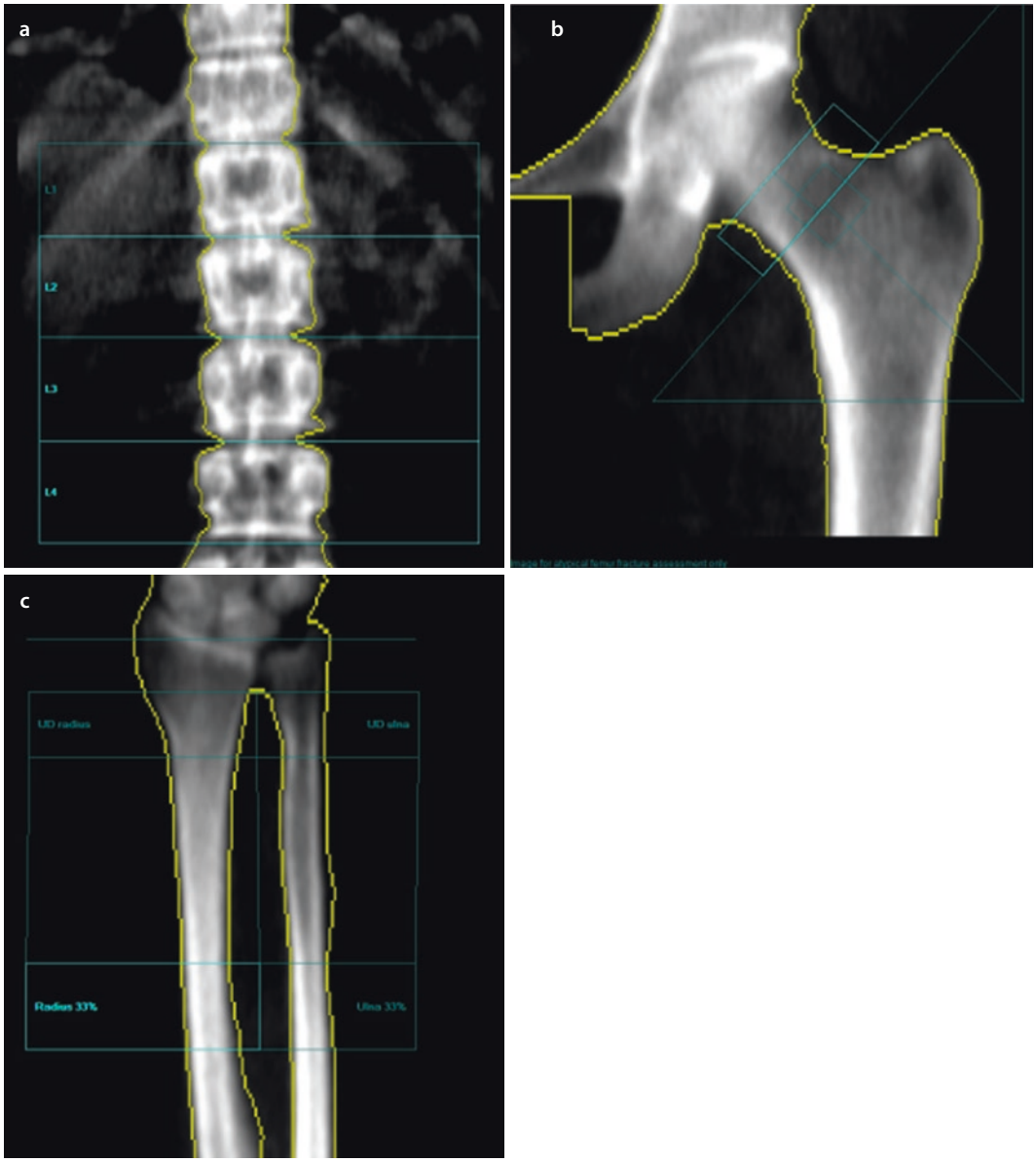

Fig. 24.2 Bone densitometry images, **a** at lumbar spine; **b** femoral neck; and **c** distal third of radius. Note that the diagnosis is not based on the images: they only show the bone region where the calculation of BMD has been done—the diagnostic information is given by the numeric values of BMD and *T*-score

Is there a suspicion of secondary osteoporosis in our case?

No. As seen from her history and physical status plus laboratory results (Table 24.3), she has probably postmenopausal osteoporosis. She has never used glucocorticoids, normal calcium plus PTH level excludes primary hyperparathyroidism, normal thyroid stimulating hormone (TSH) suggests euthyroidism, protein electrophoresis excludes myeloma, normal hemoglobin-A1c, glycated hemoglobin (HbA1c) is against diabetes and laboratory tests suggest normal liver and kidney function. There are no signs of rheumatoid arthritis, COPD (chronic obstructive pulmonary disease), or breast cancer, neither of malabsorption. Of common causes of secondary osteoporosis, only a hypercalciuria

Table 24.2 BMD, *Z*-score, and *T*-score values of our patient

	BMD (g/cm²)	*Z*-score	*T*-score
Lumbar spine (L1–4)	0.796	−2.0	−3.2
Femoral neck	0.662	−1.5	−2.7
Total hip	0.688	−1.6	−2.6
Radius	0.724	−1.5	−1.7

was shown, however, the coexisting normal PTH value doesn't suggest renal hypercalciuria (orderly accompanied by secondary hyperparathyroidism), but rather the effect of vitamin D overdosing (see later).

How do we evaluate the laboratory results of calcium metabolism?

Normal calcium, phosphate, and PTH levels in serum and normal urinary excretion of calcium are characteristic for osteoporosis. Of bone turnover markers, beta-crosslaps serum concentration mirrors the level of bone resorption and can be high-normal in osteoporosis, suggesting an active bone-losing process. For example, a former hyperthyroidism could produce high resorption and bone loss in that time, but the recovery to euthyroidism normalizes the resorption and partly normalizes bone mass. So, in our case, the low BMD can partly come from the former hyperthyroid effect but the currently upper-normal resorption marker concentration reflects a current bone-harming process other than the past hyperthyroidism. High levels of beta-crosslaps are less often accompanied by higher level of osteocalcin or alkaline phosphatase. As big overlaps exist between the ranges of healthy and osteoporotic individuals for both two turnover markers, their solely use in the diagnosis has limitations; however, they can be helpful in case of intermediate *T*-scores.

Table 24.3 Results of laboratory measurements

Value	Reference range	
Serum biochemistry:		
Calcium, total	2.52 mmol/L	2.20–2.65
Calcium, ionized	1.18 mmol/L	1.05–1.25
Phosphate	1.16 mmol/L	0.81–1.45
Creatinine	66 μmol/L	45–84
Protein, total	77.7 g/L	66–83
Albumin	49 g/L	35–52
Protein elfo: normal distribution		
Gamma-glutamyl-transferase (gammaGT)	15 IU/L	<38
Alkaline phosphatase	70 IU/L	30–120
HbA1c	4.8%	< 6.0
Urinary biochemistry: 24 hours collected urine		
Calcium concentration	4.01 mmol/L	1.7–5.3
Calcium excretion	10.03 mmol/24 h	2.5–6.2
Phosphate excretion	26.2 mmol/24 h	12.9–42
Creatinine excretion	8.54 mmol/24 h	7–16
Serum hormone measurements:		
TSH	1.711 mIU/L	0.35–4.94
PTH	31 pg/mL	10–85
25-OH-D	64.9 ng/mL	30–60
Osteocalcin	35 ng/mL	20–48
Beta-crosslaps	964 pg/mL	100–1008
(25-OH-D: 25-hydroxyvitamin-D)		

What is a basic strategy of the anti-osteoporotic therapy?

Osteoporosis is characterized by elevated bone resorption plus less elevated or even decreased bone formation, producing net

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Box 24.2 Treatment Options Against Osteoporosis

- *Depression of increased bone resorption*
  - Bisphosphonates (alendronate, zoledronate, etc.)
  - Denosumab: receptor activator of nuclear factor kappa-beta ligand (RANKL)-antibody
  - Estrogens? or selective estrogen receptor modulators (SERMs)?

and/or

- *Stimulation of insufficient bone formation*
  - Intermittent PTH-analogues

furthermore

- *Basic therapy—if necessary*
  - Calcium and/or vitamin D

and

- *Nonpharmacologic options*
  - Exercise for bones and muscles
  - Balance programs for risk reduction
  - Proper diet and lifestyle (omitting smoking, alcohol, etc.)

loss of bone in every remodeling event. The treatment methods are directed to decrease bone resorption and/or stimulate bone formation (▶ Box 24.2). The former aim can be attained by the decrease of osteoclast function through two different routes: depressing directly the resorbing ability of osteoclasts (by bisphosphonates, or transiently by estrogens) or interfering in the regulation of osteoclast production, maturation, and activation (by denosumab). Osteoblasts can be stimulated to form new bone in a more limited scope as currently the parathormone-analogue peptides are the only anabolic drugs for bone.

What is the basic therapy? Is this what all patients have to take?

The answer is yes *and* no! Supply of bone tissue with relevant amount of calcium and calcitriol (1,25-dihydroxyvitamin D) is necessary as these compounds are of prime importance for normal bone remodeling. While neither calcium nor vitamin D does not cure osteoporosis, their deficiencies inhibit the efficacy of anti-osteoporotic drugs. So, a basis of osteoporosis therapy is to ensure normal calcium supply and normal calcitriol serum concentration what is to be checked before treatment starts.

The daily recommendation is 800–1200 mg calcium, ideally achieved through dairy products. If the calcium intake is below 800 mg daily then oral supplementation should be given. For vitamin D, the measurement of 25-OH-D (25-hydroxycholecalciferol) is helpful: *if* it is below 30 ng/mL (75 nmol/L) then 800 IU vitamin D3 should be advised for the osteoporotic patient. Overdose of calcium can be associated with adverse cardiovascular events, while overdosage of vitamin D produces hypercalciuria (see lab results of our patient) and kidney stones or nephrocalcinosis.

Antiresorptive therapy: how does it work?

Bisphosphonates inhibit osteoclast function, resulting in slower bone remodeling without restoring the balance between resorption and formation. The number and size of new resorption cavities decrease quickly while intact osteoblasts form new bone into the previously formed cavities, so bone mass increases. After a time, the decreased resorption rate suppresses formation because of less number of new cavities for bone formation. Elevation of BMD reaches a plateau but low turnover rate allows less net bone loss.

- Bisphosphonates have high affinity to bone tissue, so they are concentrated in bones that has benefit for safety and long-term efficacy. Then again it is inconvenient: bisphosphonates reach well all the trabeculae but not the deep cortical bone as they are stably bound near to the surface. So, bisphosphonates exert more effects on trabecular than on cortical bone while the skeleton contains 80% compact bone and two-third of osteoporotic fractures occur at the dominantly compact peripheral bones.

- Oral bisphosphonates (alendronate, risedronate) are the initial treatment in majority of patients and are available in generic forms. The use of them should be limited to persons with more than 35 ml/min glomerular filtration rate and normal vitamin D serum level (otherwise hypocalcemia can develop). Gastrointestinal irritation may occur: this is why weekly or monthly doses and special dosing instructions are recommended; however, the adherence rate after 1 year is below 40%. In case of intolerance or contraindications intravenous bisphosphonates (zoledronate, ibandronate) or denosumab can be used.

- Denosumab is an antibody binding RANK-ligand (RANKL, receptor activator of nuclear factor kappa-beta ligand), inhibiting the osteoclast differentiation. Its antiresorptive effect differs from bisphosphonates because of no strong affinity binding to bone. Due to this, they work equally well in trabecular and cortical bone but the effect is limited to a period after which repetition is needed. Denosumab is an injection given every half year. Its important benefit is that there is no limitation for compromised renal function. Adversely, soft tissue inflammations or hypocalcemia can occur but very rarely.

- Antiresorptive medication seems highly effective in fracture prevention: in clinical studies 50–70% of vertebral, 40–56% of hip, and 25–41% of nonvertebral fractures have been prevented. The corresponding results are estimated to be halved in real life, mainly due to the low adherence rate. Adherence can be better for denosumab (injected twice a year) or for zoledronate (injected once a year).

- Estrogens and SERMs (selective estrogen receptor modulators) are much less used because of increased breast or uterine malignancy for the former and less fracture preventing efficacy for the latter.

- Recently, zoledronate has been proven to prevent fragility fractures in women with osteopenia as effectively as in osteoporosis.

? How long an antiresorptive therapy lasts?

- Bisphosphonate treatment should be reviewed after 5 years with estimating the rate of new fractures (including silent vertebrals) and reassessing fracture risk (see below). In patients who stop treatment, risk of new fractures can be elevated, and increasing turnover rate by markers (crosslaps) can be a warning signal.

- Optimal duration of denosumab therapy is still not known, as the effect was continual even after 10 years in some studies. Effect of a denosumab injection lasts for 6 months, after when a repeated dose should come within 4 weeks. Withdrawal of this therapy is associated with rebound in fracture rate: in such case, bisphosphonates can be considered.

? Why is the adherence to antiresorptives so low?

- Poor adherence is a common problem of long-term medications handling a silent disease with aiming to prevent severe future outputs (hypertension, diabetes, etc.). Osteoporosis is a good example of such case because the patient must tolerate side-effects during complaint-free years in the hope to prevent fractures later. The most frequent gastrointestinal irritations are handled by special recommendations for taking the tablet or by intravenous medication. However, the relative importance of

two rare but severe adverse effects has recently become a barrier to initiate or carry on the antiresorptive therapy.

What kinds of rare but severe adverse effects are related to antiresorptive therapy?

Atypical fractures at the femur diaphysis have been observed very rarely (1–5 cases among 10,000 bisphosphonate or denosumab users). The pathomechanism is still unclear and the risk increases over 5 years of treatment. Cortical thickening or humping of femoral diaphysis can be observed on X-ray or on DEXA scans before the fracture occurs, giving a chance to stop the drug in risky patients.

Osteonecrosis of the jaw has similarly low incidence estimated to one case among 10,000 antiresorptive users, however, it can be higher in patients taking higher doses for cancer treatment. The pathomechanism is unclear. Parallel use of glucocorticoids, wrong dental hygienic conditions, or dental surgery together with antiresorptive medication increases the risk.

Widespread and non-professional discussion of these rare adverse events in the media and insufficient responses and lazy education by the professional medicine resulted in halving of patients treated by antiresorptives in the last decade worldwide. This barrier is shocking because treating 10,000 osteoporotic patients for 3 years can prevent 1000 new fractures (including 100 hip fractures, responsible for 30% mortality within 1 year), while less than 1 atypical fracture or osteonecrosis occurs in the same group.

What are the bone forming agents?

Partial analogues of the parathyroid hormone molecule exert strong anabolic action on osteoblasts if giving intermittently (teriparatide and abaloparatide). While the exact mechanism of action is unclear, BMD spectacularly increases in trabecular bone with 65–70% risk reduction of new vertebral fractures, but not of hip fractures. The treatment is limited to 2 years because higher risk of osteosarcoma has been observed in rodents with long-term high-dose treatment (in humans only one case among one million treated patients). After stopping teriparatide treatment, the gained bone will be lost quickly, so an antiresorptive treatment needs to follow the anabolic session.

Whom to treat?

By the pharmaceutical development in the last 20 years, a broad palette of anti-osteoporotic drugs is available. The question is: who needs to be treated? On one hand, low BMD doubles the fracture risk by every 1 SD decrease of *T*-score. Nevertheless, low BMD can reflect not only a current bone loss but remnant of previous bone-losing diseases or drugs (former hyperthyroidism, glucocorticoid treatment, etc.) or insufficient development of peak bone mass in young people. On the other hand, evidences suggest that the half of low-trauma fractures occur in patients with osteopenia or normal BMD, pointing out the importance of bone features other than mass in the strength of bone. In sum, finding patients with high risk for fragility fracture is the most important requirement before treatment starts.

Above age, sex, and bone mineral density, several factors contribute significantly to fracture risk: low body mass, previous fracture, parental hip fracture, glucocorticoids, smoking, alcohol, and causes of secondary osteoporosis. Additional factors can be the early menopause, thoracic kyphosis, more than 4 cm height loss. The most effective risk factors have been composed in a calculation tool called Fracture Risk Assessment Tool (FRAX) that is available on a website (► www.shef.ac.uk/frax) free for any user. FRAX calculates the 10-year probability of hip fracture and major osteoporotic fractures in an individual. The calculation can be done with or without (hip) BMD. Further risk factors not incorporated into FRAX can influence the inter-

pretation: dose of glucocorticoids, spine BMD, falls history, and type 2 diabetes. While bone densitometry provides the diagnosis of osteoporosis as a disease, FRAX helps as an intervention threshold to initiate the treatment. Cut-off values in the United States are 3% for hip and 20% for major fractures: these limits reflect the local relations of health-economic field; however, the limits are taken in most countries worldwide. In our patient the 10 years probability is 5.2% for hip fracture and 12.2% for major osteoporotic fractures by FRAX.

How can we monitor the effectivity of treatment?

The best therapeutic answer is if no more fractures occur but it needs longer period. In the first year, the turnover markers can suggest effectivity. After 1–2 years BMD measurements will show the gain in bone mass or at least stopping bone loss. It's an important issue that FRAX is not a tool for monitoring.

What happens with male patients with osteoporosis?

Osteoporosis is not a female disease: about one-third of fragility fractures develop in men. Main issues of osteoporosis diagnosis and management are similar in both genders. Some differences originate from the andropause what comes later and less dramatically than the menopause; however, the impact of hypogonadism is very expressed in males too. Secondary osteoporosis is more frequent in males and the leading cause is the alcoholism. Estrogens are naturally out of use in male osteoporosis but testosterone is also rarely used, only in case of established hypogonadism. FRAX thresholds are the same as in females. Fracture prevention is even more important for the osteoporotic men: while their fragility fractures occur in later age, the prognosis of fracture is inferior and mortality rate is higher than in women.

Tips

The reader is advised to read the chapter on primary hyperparathyroidism (▶ Chap. 22) and the next chapter on osteomalacia (▶ Chap. 25).

Take Home Messages

- Osteoporosis is a metabolic bone disease characterized by progressive loss of bone mass and qualitative changes in microarchitecture, resulting in a high prevalence of fragility fractures.
- Beside primary, age-related osteoporosis, there are several secondary forms of osteoporosis.
- Osteoporosis is mainly diagnosed based on bone mineral density that is measured by bone densitometry. A *T*-score below −2.5 is the mainstay of diagnosis.
- The basic treatment of osteoporosis includes calcium and vitamin D supplementation.
- Antiresorptive (bisphosphonates and denosumab) and bone forming agents (parathyroid hormone derivatives) can be used in the treatment.
- Fracture risk assessment (FRAX) should be used to determine which patients should be treated.

Suggested Reading

1. Blake G, Adams JE, Bishop N. Chapter 30: DXA in adults and children. In: Rosen CJ, editor. Primer on the metabolic bone diseases and disorders of mineral metabolism. 8th ed. Somerset: Wiley; 2013. p. 249–63.
2. Compston J, Cooper A, Cooper C, Gittoes N, Gregson C, Harvey N, Hope S, Kanis JA, McCloskey EV, Poole KES, Reid DM, Selby P, Thompson F, Thurston A, Vine N. UK clinical guideline for the prevention and treatment of osteoporosis. Arch Osteoporos. 2017;12:43. https://doi.org/10.1007/s11657-017-0324-5.
3. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, Delmas P, Zoog HB, Austin M, Wang A, Kutilek S, Adami S, Zanchetta J,

Libanati C, Siddhanti S, Christiansen C. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361:756–65. https://doi.org/10.1056/NEJMoa0809493.

4. Eekman DA, van Helden SH, Huisman AM, Verhaar HJ, Bultink IE, Geusens PP, Lips P, Lems WF. Optimizing fracture prevention: the fracture liaison service, an observational study. Osteoporos Int. 2014;25:701–9. https://doi.org/10.1007/s00198-013-2481-8.
5. Kanis JA, Harvey NC, Cooper C, Johansson H, Oden A, McCloskey EV. A systematic review of intervention thresholds based on FRAX: a report prepared for the National Osteoporosis Guideline Group and the International Osteoporosis Foundation. Arch Osteoporos. 2016;11:25. https://doi.org/10.1007/s11657-016-0278-z.
6. Kanis JA, Harvey NC, McCloskey E, Bruyère O, Veronese N, Lorentzon M, Cooper C, Rizzoli R, Adib G, Al-Daghri N, Campusano C, Chandran M, Dawson-Hughes B, Javaid K, Jiwa F, Johansson H, Lee JK, Liu E, Messina D, Mkinsi O, Pinto D, Prieto-Alhambra D, Saag K, Xia W, Zakraoui L, Reginster J-Y. Algorithm for the management of patients at low/middle/high risk of osteoporotic fracture: a global perspective. Osteoporos Int. 2019;31:1–12. https://doi.org/10.1007/s00198-019-05176-3.
7. Kanis JA, Cooper C, Rizzoli R, Reginster JY. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2019;30:3–44. https://doi.org/10.1007/s00198-018-4704-5.
8. Kraenzlin ME, Meier C. Parathyroid hormone analogues in the treatment of osteoporosis. Nat Rev Endocrinol. 2011;7:647–56. https://doi.org/10.1038/nrendo.2011.108.
9. Rizzoli R, Burlet N, Cahall D, Delmas PD, Eriksen EF, Felsenberg D, Grbic J, Jontell M, Landesberg R, Laslop A, Wollenhaupt M, Papapoulos S, Sezer O, Sprafka M, Reginster JY. Osteonecrosis of the jaw and bisphosphonate treatment for osteoporosis. Bone. 2008;42:841–7. https://doi.org/10.1016/j.bone.2008.01.003.
10. University of Sheffield. FRAX fracture risk assessment tool. 2008. https://www.sheffield.ac.uk/FRAX/.
11. Watts NB. Fundamentals and pitfalls of bone densitometry using dual-energy X-ray absorptiometry (DXA). Osteoporos Int. 2004;15:847–54. https://doi.org/10.1007/s00198-004-1681-7.

Osteomalacia

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Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_25

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Opening

Osteomalacia is a metabolic bone disease characterized by ineffective mineralization of osteoid in the remodeling of adult bone. It is called rickets in growing children if this process is accompanied by the deficient mineralization of cartilage in growth plates. The disease derives from calcium deprivation due to low calcium intake by any reason, including vitamin D deficiency. The vast majority of cases are explained by nutritional or lifestyle factors, but other alterations (genetic, renal, malignant, and iatrogenic) can also be found. The main clinical outputs are the painful bones and muscles and increased fragility in adults, while rickets of children can be associated with delayed development, deformity, and pain of long bones and pelvis, and sometimes hypocalcemia. Dilated cardiomyopathy is not rare, being responsible for increased mortality in both age groups. Osteomalacia is a heavily underdiagnosed disease with globally rising incidence, for example, its prevalence in Europe is estimated as high as 25% in autopsies (mostly unrecognized). If thinking about it, the diagnosis is easy and the treatment is successful. Moreover, nutritional osteomalacia is a preventable disease.

Definition of the Disease

Vitamin D deficiency is maybe the most common human nutritional disease, leading to decreased absorption of calcium and phosphate from the gut that is frequently combined with deficient intake of calcium by foods. Hereby, calcium deprivation develops and the extracellular calcium concentration tends to decrease. However, hypocalcemia is a life-threatening condition, so a robust compensation through the secondary overproduction of parathyroid hormone (PTH) will promptly start and restore normocalcemia by using two sources. Firstly, PTH increases the reabsorption and decreases the excretion of calcium in the distal renal tubule. Secondly, PTH stimulates osteoblasts to produce soluble RANKL (receptor activator of nuclear factor kappa-beta ligand) that activates production and maturation of the osteoclasts, increasing bone resorption and liberating calcium ions. A further effect of PTH decreases tubular reabsorption and increases urinary excretion of phosphate. The subsequent hypophosphatemia finally disturbs the intricately balanced regulatory triangle of PTH and FGF-23 (fibroblast growth factor-23) and calcitriol (1,25-dihydroxy-cholecalciferol). It is presumed that hypophosphatemia contributes dominantly to the defective mineralization of osteoid.

In summary, osteomalacia is a complex disturbance of bone remodeling in the calcium-deprived adults, consisting of increased bone resorption and osteoid overproduction but a defective mineralization of the new osteoid. If it happens in childhood and involves the cartilage of growing plate then it is called rickets.

Vitamin D deficiency has a wide clinical spectrum from mild cases (incident laboratory alterations only) to severe clinical appearance (osteomalacia: bone complaints and fractures, attended by laboratory and radiologic signs).

Case Presentation

A 34-year-old man has been referred to the metabolic bone clinic because he complained about muscle weakness and bone pain, particularly in his limbs but also in the pelvic region and lower extremities of both sides. His complaints started 2 years before and became gradually from bad to worse. In the last year, he had two falls that did not lead to fractures. His family doctor excluded hypokalemia. Primary hyperparathyroidism (normal calcium and PTH levels in

serum), chronic kidney disease (normal glomerular filtration rate), and a neurologic examination (with normal spine CT) excluded the neurologic background of the problem. X-ray of the legs found a transverse lucency (like a fracture line), partly crossing his left femoral shaft. This finding was recorded as an imminent fracture and a metal screw was inserted into the bone to prevent the completion of femoral fracture. Orthopedic surgery was done 5 months before, followed by rehabilitation; however, he still suffered from disability. The week before his admission, the control X-ray found the operated femur in good condition, but a similarly partial crossing line was observed at the opposite femur in symmetrical position as it was previously seen on the left side.

There were neither previous diseases nor regular medications or alcohol consumption in his medical history. Gonadal functions were self-reportedly going well. He worked in an office and spent his leisure time with computer games.

Our physical examination didn't find specific alterations except the remnants of the femoral surgery, and mild scoliosis at the cervico-thoracic spine.

Why just the osteomalacia is suspected and not an osteoporosis?

The first argument is that osteoporosis is a silent disease not associated with bone pain. Secondly, osteoporosis causes low-trauma fractures what is not in our case: his two falls were not followed by fractures. Lastly, the main risk factors for osteoporosis like female sex, older age, signs of hypogonadism, history of osteoporogenic diseases or medications, and higher alcohol intake are all absent in this story.

On the other hand, his case shows a number of signs pointing to a potential osteomalacia. He is a young man living dominantly in closed spaces, without sports and sunshine exposure. The main complaint is the bone pain without specific reasons and localized particularly in the proximal part of the lower extremities. Muscles are also sensitive and painful, maybe associated with deficient balance as he fell twice. Complaining about to bones and muscles of this localization is pretty characteristic for osteomalacia. Finally, the traversing but not completely crossing fracture lines in the long bones form a suspicion of having osteomalacia rather than osteoporosis.

What is the etiology of osteomalacia and how can we diagnose it?

To answer this question, firstly an overview of *vitamin D metabolism* is recommended because this basic knowledge makes clear the etiologic and diagnostic considerations. Humans can obtain vitamin D3 (cholecalciferol) naturally from a narrow spectrum of dietary foods like oily fish (salmon, sardine, mackerel, and tuna) and cod liver oil, or in smaller amount from pork, beef liver, and eggs. Another source can be the synthesis of D3 from its provitamin (7-dehydrocholesterol) in the skin exposed to sunlight. Vitamin D2 (ergocalciferol) is found in mushrooms and yeasts or synthesized from ergosterol.

Vitamin D enters the circulation and reaches the liver and the kidney to get over two activating steps. A vitamin D binding protein helps this transportation while a part of cholecalciferol is stored in adipose tissues. In the liver, a 25-hydroxylase enzyme (CYP2R1) produces 25-hydroxyvitamin D (25-OH-D) that has only very low biologic activity for the vitamin D-like physiologic effects. It's an important issue that 25-hydroxylation goes under substrate-regulation only: if there is substrate and there is liver tissue than the process will occur. This feature explains that vitamin D status can be assessed precisely by measuring the plasma 25-OH-D level.

The true activation of vitamin D takes place in the kidney where a second hydroxylation will be done by the 1α-hydroxylase (CYP27B1) enzyme. The final product is the calcitriol (1,25(OH)2-cholecalciferol) what exerts 1000-fold stronger effects than

the basic vitamin D. Calcitriol gets an extraordinary biological respect because of its amazing effectivity that ensures its importance and risks in the same time. So, it is not surprising that 1α-hydroxylation goes under strict and multiple regulatory control. The main regulators are PTH (directly, and indirectly through hypophosphatemia) and FGF-23, but many hormones (estrogens, glucocorticoids, etc.), and what is more, the sympathetic nervous system can also modulate its activity. On the other hand, a negative feedback saves it from overactivity as calcitriol suppresses the 1α-hydroxylase. Moreover, another enzyme (24-hydroxylase, CYP24A1) makes inactive forms like the 24,25(OH)2-D or 1,24,25(OH)3-D.

In summary, vitamin D enters the body by foods, then passes through more activating steps, and finally produces a classical hormone: it is made from pre-materials, the formation goes under regulation, its effect will be exerted far (bone, gut, and immune system) from the site of production (liver and kidney), and the molecule is transported to the sites of effect by the circulation. Yes, we eat a vitamin—but form a D-hormone what is the true carrier of the vitamin D-related physiologic effects.

It should be also clear now that measurement of the calcitriol plasma level will not inform about the vitamin D status of a patient as its concentration is being changed continuously by the complicated regulatory systems.

Osteomalacia has been depicted as a bone disease due to calcium deprivation, but now we are discussing vitamin D: how are they linked?

The ideal amount of daily calcium intake for adult humans is about 1000 mg. In modern societies, people consume about 600–800 mg daily what is less but not very far from the ideal supply. The problem lies in the crucial role of vitamin D in the intestinal calcium absorption that is very effective in the presence of calcitriol but can be very low without the help of vitamin D. The level of calcium deprivation what is enough to develop osteomalacia can be originated from a severely low intake of calcium by foods, or more probably from a deficient enteral absorption of calcium due to the lack of calcitriol effect, or from the combination of both.

So, understanding the basic considerations—what are the main causes of osteomalacia?

Table 25.1 presents some conditions leading to osteomalacia. Insufficient intake or absorption of vitamin D, low exposure to sunshine, chronic kidney diseases, elder age, obesity, and their combinations make the highest risk for osteomalacia. Geographic position of the habitat has the most determining power: north or south from the 34° latitude is related to seasonal or continuous lack of ultraviolet B spectrum of sunlight. Dark skin, the culture of full-body clothing, and widespread use of sunscreen raise the risk even further. Please note that the insufficient effect of vitamin D to stimulate enteral calcium uptake alone can be enough to initiate the bone pathology; however, its effect is more expressed in parallel case of low calcium supply.

How shall we recognize vitamin D insufficiency?

It is important to understand the difference between vitamin D deficiency and osteomalacia. The former is an extremely frequent nutritional insufficiency which—in severe cases, or in combination with calcium deprivation—can lead to the specific bone disease called osteomalacia.

The serum level of 25-OH-D (total D, including D3 and D2) is regarded as the best marker of vitamin D status. The lower border of the normal reference range is a manner of dispute worldwide. Some experts define it as 30 ng/mL (75 nmol/L) because below this threshold a secondary hyperparathyroidism will be activated. Other opinions vote to 20 ng/mL (50 nmol/L) as a value better characterizing the distribution of the healthy

Table 25.1 Osteomalacia—main causes of practical importance

A. Lack of relevant calcium input	
Low calcium intake by foods	
Low calcium absorption in the gut: malabsorption syndrome	
B. Lack of relevant vitamin D effects (low calcium absorption)	
Decreased vitamin D supply:	Low intake by foods, malabsorption syndrome
Decreased vitamin D production:	Reduced sunlight exposure Dark skin (less sunlight) Obesity (lipophyl store) Older age (older skin and kidney)
Altered D-activation:	Chronic kidney disease Nephrosis (loss of binding protein) Chronic liver disease Pregnancy Hypophosphatemia: tumor-induced[a], hyperparathyroidism, Fanconi's syndrome[b], renal tubular acidosis, sarcoidosis, hypophosphatemic rickets (X-linked or autosomal), vitamin D dependent rickets type 1A (1α-hydroxylase deficiency)
Increased catabolism (via P-450):	Medications (antiepileptics, antivirals, antirejection drugs, glucocorticoids, phenobarbital, isoniazid, rifampicin, and theophylline), hyperthyroidism, granulomatous disorders
Deficiency in vitamin D responsiveness (receptor failures and vitamin D-resistant rickets)	

[a]Tumor-induced osteomalacia or oncogenic osteomalacia is a rare endocrine paraneoplastic syndrome associated with severe hypophosphatemia that is mostly observed with small, often benign mesenchymal tumors secreting FGF-23

[b]Fanconi's syndrome is a combined proximal renal tubulopathy comprising phosphaturia, glucosuria, aminoaciduria, proteinuria, and proximal renal tubular acidosis

population. All agree in the threshold of 10 ng/mL (25 nmol/L) below which it is called vitamin D deficiency while between 10 and 20 (or 10–30) ng/mL it is referred to as vitamin D insufficiency. Anyway, the severity of the condition is described also by the associated alterations in calcium metabolism as it is shown in Table 25.2. Serum calcium level decreases slightly into the lower half of normal range as secondary hyperparathyroidism compensates, increasing the PTH and lowering the phosphate levels. Urinary calcium excretion is characteristically low due to less filtrated and more reabsorbed calcium in the kidney. Urinary phosphate output is also decreased. The starting involvement of the bone is shown by elevated turnover markers (beta-crosslaps, osteocalcin, and alkaline phosphatase—see in detail in the osteoporosis chapter (▶ Chap. 24)).

Vitamin D insufficiency is associated with poor clinical symptoms like generalized fatigue (commonly misdiagnosed as fibromyalgia, polymyalgia, or chronic fatigue syndrome) and proximal muscle weakness in legs. In rickets, irritability, restlessness, and flabby muscles can be the first signs.

How can osteomalacia be diagnosed?

If the calcium- and/or vitamin D deprivation process doesn't stop, osteomalacia will develop gradually. It is featured by alterations in calcium metabolism (higher levels of

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Table 25.2 Results of laboratory measurements

	Value	Reference range	
Serum biochemistry:			
Calcium, total	2.28 mmol/L	2.20–2.65	
Calcium, ionized	1.02 mmol/L	1.05–1.25	
Phosphate	0.51 mmol/L	0.81–1.45	
Creatinine	69 μmol/L	45–84	
Protein, total	72.2 g/L	66–83	
Albumin	42 g/L	35–52	
Gamma-glutamyl-transferase (gammaGT)	21 IU/L	< 38	
Alkaline phosphatase	234 IU/L	30–120	
Urinary biochemistry:	24 hours collected urine		
Calcium excretion	0.42 mmol/24 h	2.5–6.2	
Phosphate excretion	11.2 mmol/24 h	12.9–42	
Creatinine excretion	9.50 mmol/24 h	7–16	
Serum hormone measurements:			
TSH	1.94 mIU/L	0.35–4.94	
PTH	188 pg/mL	10–85	
25-OH-D	7.9 ng/mL	30–60	
Osteocalcin	55 ng/mL	20–48	
Beta-crosslaps	1211 pg/mL	100–1008	
Bone densitometry			
Z-score at	*Lumbar spine*	*Femoral neck*	*Forearm*
	-2,3	-2,9	-3,3

(For the explanation of *Z*-score, see the osteoporosis chapter (▶ Chap. 24))

PTH and alkaline phosphatase, very low urinary calcium), followed by deformations in bone remodeling and later in bone's shape, producing clinical symptoms, physical alterations, and specific radiologic signs. The mass of osteoid increases but its mineralization decreases that will soften the bone. Sometimes it can lead to fractures but more frequently to deformations (e.g., curving of long bones) and bone pain. In osteomalacia, the throbbing and aching bone pain is characteristic; specific signs are the tenderness on sternal compression and the waddling gait and hip pain. In rickets, a lot of symptoms help the diagnosis: head sweating, wide open fontanelles, craniotabes, frontal bossing, and so on—see in Suggested Reading.

Earlier, iliac crest bone biopsy has been the gold standard for establishing osteomalacia but now it should be reserved for dubious cases because typical X-ray findings can prove the diagnosis in the vast majority of patients. Spine radiographs show decreased distinctness of vertebral trabeculae that is a direct consequence of decreased osteoid mineralization. Another classic radiologic finding is the Looser zone that represents a poorly repaired insuffi-

ciency fracture (pseudofracture). On X-ray or on bone scintigraphy, it is seen symmetrically at the femoral shafts or at hip rami.

Bone densitometry is usually decreased in osteomalacia, as even 20% of the bone mineral mass can be lost. Experts suggest that bone loss is more pronounced at peripheral bones due to secondary hyperparathyroidism. The fracture risk assessment tool (FRAX; see in osteoporosis chapter (► Chap. 24)) is not fully sensitive to osteomalacia because of a different spectrum of risk factors.

Are there any complications of this disease?

Long-term osteomalacia will develop irreversible disability due to final bone deformations. Looser zones as insufficiency fractures are responsible for the bone pain. Vertebral compression fractures are less common, but they can contribute to kyphoscoliosis, significantly decreasing the quality of life and increasing mortality. Dilated cardiomyopathy may develop particularly in case of frequent hypocalcemic episodes and more probably in children, contributing to sudden death—the significance of this problem in adults is still unclear.

If they have developed, most of these complications remain even in case of successful treatment of osteomalacia. On the contrary, Looser zones (pseudofractures) have a better prognosis: they can be completely healed by a long-term vitamin D therapy. For this reason, Looser zones don't need surgery (as unfortunately happened in our case) but need vitamin D (as it was done with the patient's second pseudofracture).

How to treat osteomalacia?

Firstly, it is important to put down that nutritional osteomalacia (the vast majority of cases) is a curable disease. The treatment target is to eliminate the calcium deprivation in bone by restoring the calcium supply. For this aim, the first thing to do is ensuring at least the normally required amount of calcium—dominantly by dairy products or supplemented by calcium salt medications if needed. However, in most cases the calcium absorption also needs restoration by vitamin D supplementation.

The dose and strategy of vitamin D treatment is controversial. Some scientific societies and consensus papers suggested big doses for saturation (6000–50,000 IU once a week, for 6–8 weeks), followed by 1500–2000 IU for maintenance. What's more, really large doses (200.000–500.000 IU, once in every 6 or 12 months) have also been recommended in the hope for a better adherence to the therapy. However, recent studies revealed that these high doses can initiate a transient bone loss and increased fracture rate in the first half year, and the rebuilding of bone and reducing fragility was shown only in the second half of the treatment year. A more tolerant and safe strategy gives longer time to bone healing: treatment starts with 3000–6000 IU every day and after 6 weeks the 25-OH-D level should be monitored. The higher dose is given until the 25-OH-D level is normalized. After this, a daily dose of 1000–2000 IU is given continuously. The higher doses are proposed to patients with increased risk like in obesity or pregnancy.

Vitamin D3 is in use dominantly because its half-life is longer than that of D2. Absorption of orally given vitamin D is very good while it is less adequate via the parenteral route. Duration of treatment lasts probably lifelong since the underlying risk (latitude, dark skin, culture of clothing, etc.) is unlikely to change. In case of low adherence or a drug-holiday, osteomalacia has a tendency for recurrence.

Is there any unwanted consequence of vitamin D treatment?

Unfortunately, yes there is. The problem lies in the different effectivity of calcitriol in the target organs that may be complicated by the diversity of patients in the vitamin D transport and receptors. Vitamin D treat-

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ment should be monitored by checking the 25-OH-D level in the serum: the goal is to maintain this value between 30 and 60 ng/mL (75–150 nmol/L) as bone healing could be the best by this range. However, in some patients, this set of 25-OH-D level can be associated with disproportionately increased calcium absorption in the gut, and this could lead to hypercalcemia. As the maintenance of normal calcium concentration has a superb biologic significance, the hypercalcemia will be prevented by excreting more calcium in the urine.

Indeed, vitamin D alone causes hypercalcemia very rarely: it occurs only with the use of high doses what should be avoided. Nevertheless, hypercalciuria can be seen in 10–20% of cases with long-term vitamin D treatment. Increased calcium excretion is known as the main risk factor for kidney stone production; moreover, a silent but fatal nephrocalcinosis may also develop. In case of hypercalciuria, the dose of vitamin D should be halved, and calciuria is to be monitored regularly. Combination therapy with thiazides that reduce calcium excretion can also be an option, but it needs strict control of serum calcium level because of the hazard of hypercalcemia.

What methods are available for the prevention of osteomalacia?

Nutritional osteomalacia and rickets are fully preventable diseases. Supplementation of infants and pregnant women, promoting vitamin D and calcium intake for all age groups (particularly for elders), education concerning risk groups and conditions, and food fortification are the main methods what are applied and studied worldwide for the prevention (see more in Suggested Reading).

Tips

The reader is advised to read the chapter on primary hyperparathyroidism (▶ Chap. 22) and the preceding chapter on osteoporosis (▶ Chap. 24).

Take Home Messages

- Osteomalacia is a complex disturbance of bone remodeling in the calcium-deprived adults, consisting of increased bone resorption and osteoid overproduction but a defective mineralization of the new osteoid.
- Low intake or insufficient absorption of calcium contributes to development of osteomalacia; however, the severe vitamin D deficiency is the main factor leading to this disease.
- Insufficient intake or absorption of vitamin D, low exposure to sunshine, chronic kidney diseases, elder age, obesity, and their combinations make the highest risk for osteomalacia.
- The serum level of 25-OH-D (total 25-hydroxyvitamin D) is regarded as the best marker of vitamin D status.
- Osteomalacia can lead to fractures but more frequently to deformations (e.g., curving of long bones) and bone pain. In osteomalacia, the throbbing and aching bone pain is characteristic. Looser zones (pseudofractures) of the long bones are typical radiologic signs.
- The treatment of osteomalacia starts with 3000–6000 IU every day for 6 weeks and the 25-OH-D level should be monitored. After the 25-OH-D level is normalized, a daily dose of 1000–2000 IU is given continuously. Oral vitamin D is recommended.
- It is important to avoid the overdosing of vitamin D in the treatment of osteomalacia: while hypercalcemia is a rare consequence, hypercalciuria (the main risk factor of kidney stones or nephrocalcinosis) can be frequently seen if using higher doses.

Suggested Reading

1. Bischoff-Ferrari HA, Shao A, Dawson-Hughes B, Hathcock J, Giovanucci E, Willet WC. Benefit-risk assessment of vitamin D supplementation. Osteoporos Int. 2010;21:1121–32. https://doi.org/10.1007/s00198-009-1119-3.

2. Charoenngam N, Shirvani A, Holick MF. Vitamin D for skeletal and non-skeletal health: what we should know. J Clin Orthop Trauma. 2019;10:1082–93. https://doi.org/10.1016/j.jcot.2019.07.004.
3. Institute of Medicine. Dietary reference intakes for calcium and vitamin D. Washington, DC: The National Academies Press; 2011.
4. Munns CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K, Michigami T, Tiosano D, Mughal MZ, Mäkitie O, Ramos-Abad L, Ward L, DiMeglio LA, Atapattu N, Cassinelli H, Braegger C, Pettifor JM, Seth A, Idris HW, Bhatia V, Fu J, Goldberg G, Sävendahl L, Khadgawat R, Pludowski P, Maddock J, Hyppönen E, Oduwole A, Frew E, Aguiar M, Tulchinsky T, Butler G, Högler W. Global consensus recommendations on prevention and management of nutritional rickets. Horm Res Paediatr. 2017;85(2):83–106. https://doi.org/10.1159/000443136.
5. Uday S, Högler W. Nutritional rickets and osteomalacia in the twenty-first century: revised concepts, public health, and prevention strategies. Curr Osteoporos Rep. 2017;15:293–302. https://doi.org/10.1007/s11914-017-0383-y.

Diseases of the Adrenal

The adrenal gland is composed of two different parts. The adrenal cortex is of mesodermal origin and secretes steroid hormones involved in the regulation of pivotal homeostatic mechanisms such as electrolyte balance (mineralocorticoids) and stress, inflammation, and metabolism. (glucocorticoids). Steroid hormones with androgenic activity are also produced by the cortex. The adrenal medulla is of ectodermal origin and secretes catecholamines including adrenaline (epinephrine) and noradrenaline (norepinephrine) involved in the sympathetic stress response.

Adrenal tumors are quite common and are often discovered incidentally (► Chap. 26). Most of the adrenal incidentalomas are benign and hormonally inactive adrenocortical tumors; however, hormone-secreting and malignant tumors (adrenocortical cancer, ► Chap. 30) are associated with significant morbidity and mortality.

Overproduction of adrenocortical hormones, that is, cortisol (adrenal Cushing's syndrome, ► Chap. 27) and aldosterone (► Chap. 28), and deficiency of adrenocortical hormones (Addison's disease, ► Chap. 31) are discussed in detail. The autonomous overproduction of aldosterone (primary aldosteronism), which is mostly caused by a unilateral aldosterone-producing adenoma (Conn's syndrome) or bilateral adrenal hyperplasia, is the most common cause for secondary hypertension. Secondary aldosteronism (► Chap. 29) can be observed in various pathologies that include both common and rare diseases. Autoimmune polyendocrine syndromes including primary adrenal insufficiency are presented in ► Chap. 31.

► Chapters 32, 33, 34, and 35 are dedicated to adrenocortical steroid biosynthetic enzyme deficiencies leading to different forms of congenital adrenal hyperplasia. 21-hydroxylase deficiency is the most common that is discussed in three chapters: salt-wasting and simple

virilizing forms are diagnosed in childhood, whereas the diagnosis of the more common late onset form is usually established in adults. ► Chapter 35 presents the very rare 17α-hydroxylase/17, 20-lyase deficiency.

Another rare disease, glucocorticoid resistance due to glucocorticoid receptor defects, is briefly discussed in ► Chap. 36.

The focus of ► Chaps. 37 and 38 are adrenomedullary tumors, that is, pheochromocytoma and paraganglioma (extraadrenal pheochromocytoma). ► Chapter 38 presents malignant paraganglioma and its management.

Contents

Adrenal Incidentaloma

Prerna Dogra and Irina Bancos

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_26

Opening

This chapter will focus on the diagnosis and management of incidentally discovered adrenal tumors.

26

Definition of the Disease

Adrenal incidentaloma (AI) is an adrenal mass discovered serendipitously on cross-sectional abdominal imaging performed for indications other than suspected adrenal pathology. Over the last two decades, high-resolution imaging, along with its widespread use, led to a significant increase in the incidence of AI. In a recent population study, standardized incidence rates of adrenal tumors increased tenfold between 4.4 per 100,000 persons in 1995 and 47.8 per 100,000 persons in 2017, mainly due to incidental discovery of small adrenocortical adenomas in patients >40 years. Radiological series describe a 5–7% prevalence of AI on cross-sectional abdominal imaging. Adrenal tumors are usually diagnosed in the 5th to 6th decade, with almost equal sex distribution (55% in women). In contrast, adrenal tumors, and especially AIs, are very uncommon in children, representing only 1% of all adrenal tumor diagnoses.

Case Presentation

A 55-year-old postmenopausal woman presents to the clinic to discuss the findings of an abdominal computed tomography (CT) scan performed for nonspecific abdominal pain that has since resolved. Incidentally, a 3.7 cm right homogeneous adrenal mass was discovered, with smooth borders and an unenhanced attenuation of 23 Hounsfield units (HU) (Fig. 26.1). She reports progressive weight gain of around 4 kg over the last 12 months. Patient's medical history is remarkable for type 2 diabetes mellitus, hypertension, and obesity (BMI 33.5 Kg/m^2). Family history is negative for endocrinopathies or malignancies. Patient's medications include metformin 1000 mg two times a day, glipizide 10 mg once a day, hydrochlorothiazide 25 mg once a day, and lisinopril 20 mg once a day. Vital signs include heart rate 80 beats per minute, blood pressure 130/80 mmHg, respiratory rate 16 breaths per minute, oxygen saturation 97% on room air, and temperature 97.8 degrees Fahrenheit. On physical examination, there is absence of rounded face, supraclavicular or dorsocervical fat pads, centripetal obesity, abdominal striae, ecchymosis, or hirsutism. Lab work is noted for unremarkable comprehensive metabolic panel and glycosylated hemoglobin A1c (HbA1c) 6.8%.

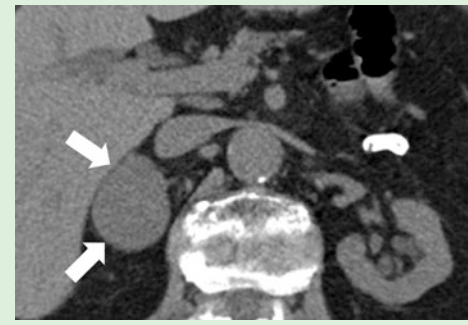

Fig. 26.1 Unenhanced CT revealed an incidentally discovered right adrenal mass (3.7 cm, Hounsfield units = 23)

What is the likely etiology of adrenal mass?

Population-based data demonstrate that the majority of adrenal tumors represent adrenocortical adenomas (84%) or other benign adrenal tumors, such as myelolipomas or cysts (6.6%), while malignant adrenal tumors (▶ Chap. 30) and pheochromocytomas (▶ Chap. 37) represent 8.6% and 1%, respectively (◘ Table 26.1). (Myelolipoma is an invariably benign tumor consisting of fat and bone marrow elements.) In endocrine clinics, the proportion of patients diagnosed with pheochromocytomas is higher, at 3–7%. The most common malignant adrenal mass evaluated in the endocrine clinic is adrenocortical carcinoma (3–8% of all tumors); however, in a population setting, most malignant adrenal tumors are metastases. Clinical, imaging, and hormonal phenotype can be diagnostic or suggestive of a particular etiology (◘ Table 26.1 and ◘ Fig. 26.2).

What should be done next?

In any patient with adrenal mass, two crucial questions need to be answered: (A) Is the adrenal mass malignant? (B) Is the adrenal mass hormonally active? (◘ Fig. 26.3) The answer to these questions is critical in establishing further management plan.

Is the adrenal mass malignant?

Certain clinical and imaging variables help make or exclude the diagnosis of adrenal malignancy. For example, history or active extra-adrenal malignancy raises the likelihood of the indeterminate adrenal mass to be an adrenal metastasis. Presentation with hormone excess suggests either benign or malignant cortical adrenal tumor (adrenal adenoma or carcinoma) or pheochromocytoma. Combined adrenal hormone excess, such as concomitant cortisol and androgen excess, is strongly suggestive of adrenocortical carcinoma. Personal or family history of a genetic predisposition such as Von Hippel-Lindau syndrome (▶ Chap. 52), multiple endocrine neoplasia type 2 (▶ Chap. 51), or neurofibromatosis type 1 is suggestive of pheochromocytoma (◘ Table 26.1).

Imaging phenotype

Imaging phenotype can be especially helpful in making the diagnosis of malignancy (◘ Table 26.2). The prevalence of malignancy in large adrenal tumors (>4 cm) is much higher than in smaller adrenal tumors (30% vs 3%). Most adrenocortical carcinomas are >6 cm at the time of diagnosis, while adrenocortical adenomas are uncommonly larger than 4 cm. However, tumor size has poor accuracy in diagnosing adrenal metastases or non-cortical benign tumors such as myelolipomas (◘ Fig. 26.2 and ◘ Table 26.1). Measurement of *HU on unenhanced CT* is the imaging of choice in the evaluation of adrenal tumors. The higher the lipid content of the mass, the lower is the density and, hence, the HU. HU <10 in a homogeneous adrenal mass confidently excludes malignancy or pheochromocytoma. However, while most benign adrenal adenomas are lipid-rich and present with HU < 10 HU, around 40% of adrenocortical adenomas are lipid-poor (HU > 10) and thus are indeterminate on imaging. Notably, any heterogeneous lesion should be considered indeterminate. CT characteristics suggestive of malignancy also include irregular borders, local invasion, and necrosis. *Contrast-enhanced washout CT* has lower evidence as far as diagnostic accuracy in adrenal tumors. All adrenal masses demonstrate rapid uptake of the contrast; however, malignant tumors demonstrate a slower washout when compared to the rapid washout of benign tumors. As such, relative washout of >40% and absolute washout >60% at 10 to 15 minutes after intravenous contrast administration is suggestive of a benign adrenal mass. *Magnetic resonance imaging (MRI)* relies on the out-of-phase loss of signal intensity on chemical shift analysis in diagnosis of adrenocortical adenomas. Although MRI offers the advantage of avoiding ionizing radiation and contrast medium, the evidence for its use is limited to a very few studies without a standardized

Table 26.1 Presentation and management of adrenal tumors

	Adrenocortical adenoma	Other benign mass	Adrenocortical carcinoma	Other malignant mass	Pheochromocytoma
Prevalence (population)	84%	7%	0.3%	8%	1%
Prevalence (endocrine clinic)	85–90%	3–7%	3–8%	1–3%	3–7%
Mode of discovery	Most: incidental	Most: incidental Minority: abdominal mass effect	Incidental: 40% Symptoms of Hormone excess: 40% Abdominal mass effect/ other: 20%	Cancer staging: 50% Incidental: 30% Abdominal mass effect/Other: 20%	Incidental: 60% Symptoms of Hormone excess: 30% Genetic screening: 10%
Tumor size	Usually <4 cm	Variable	Usually >6 cm	Variable	Usually >4 cm, variable (smaller when discovered on genetic screening)
Tumor laterality	15–20% bilateral	5–10% bilateral	<0.1% bilateral	20–40% bilateral	5–10% bilateral (if genetic predisposition, such as *VHL, MEN2, NF1, etc.*)
Unenhanced computed tomography (Hounsfield units, HU)	HU <10: 50–60% HU 10–20: 20–30% HU >20: 10–20%	HU: variable HU <0: myelolipomas HU >100: calcifications	HU > 20 (usually >30 HU)	HU > 20 (usually >30 HU)	HU > 20 (usually >30 HU)
Magnetic resonance imaging	Chemical shift: present – 60–80% Chemical shift: absent – 20–40%	Chemical shift: absent except for myelolipomas	Chemical shift: absent	Chemical shift: absent	Chemical shift: absent
FDG positron emission tomography	FDG uptake – usually absent (may be present in functioning adrenal adenomas)	FDG uptake – absent	FDG uptake – present	FDG uptake – usually present (may be absent in small metastases)	FDG uptake – present

	Adrenocortical adenoma	Other benign mass	Adrenocortical carcinoma	Other malignant mass	Pheochromocytoma
Tumor growth	Usually <1 cm in 1 year	Usually <1 cm in 1 year	Usually >1 cm in 3–6 months	Usually >1 cm in 3–6 months	Usually <1 cm in 1 year
Adrenal hormone excess	50–60% hormonally inactive 30–50% mild autonomous cortisol secretion 5–10% primary aldosteronism 1–3% overt Cushing's syndrome	None unless concomitant adrenal adenoma (21OHD CAH should be considered if myelolipomas)	Standard of care tests – abnormal in 50–79%, most common androgen and cortisol excess Urine steroid metabolomics positive in 95%	None (consider primary adrenal insufficiency if bilateral adrenal metastases)	90% catecholamine excess; however, silent pheochromocytomas may occur, especially in smaller lesions
Prognosis	Tumor growth of at least 1 cm may occur in 5%, <0.1% risk of malignant transformation, and < 0.5% risk of new adrenal hormone excess	Tumor growth with abdominal mass effect occurs in 16% of myelolipoma	Open adrenalectomy with R0 resection carries the highest chance of remission Prognosis depends on stage, R0 resection, and KI67 index	Prognosis depends on the type of extra-adrenal malignancy	Excellent prognosis if discovered early and properly treated (including optimal preparation for surgery) Metastatic disease in 10% of cases, most with indolent disease

FDG Fluorodeoxyglucose, *HU* Hounsfield unit, *VHL* Von Hipple-Lindau, *MEN2* multiple endocrine neoplasia type 2, *NF1* neurofibromatosis type 1, *21OHD CAH* 21-hydroxylase deficiency congenital adrenal hyperplasia, *R0 resection* microscopically margin negative resection

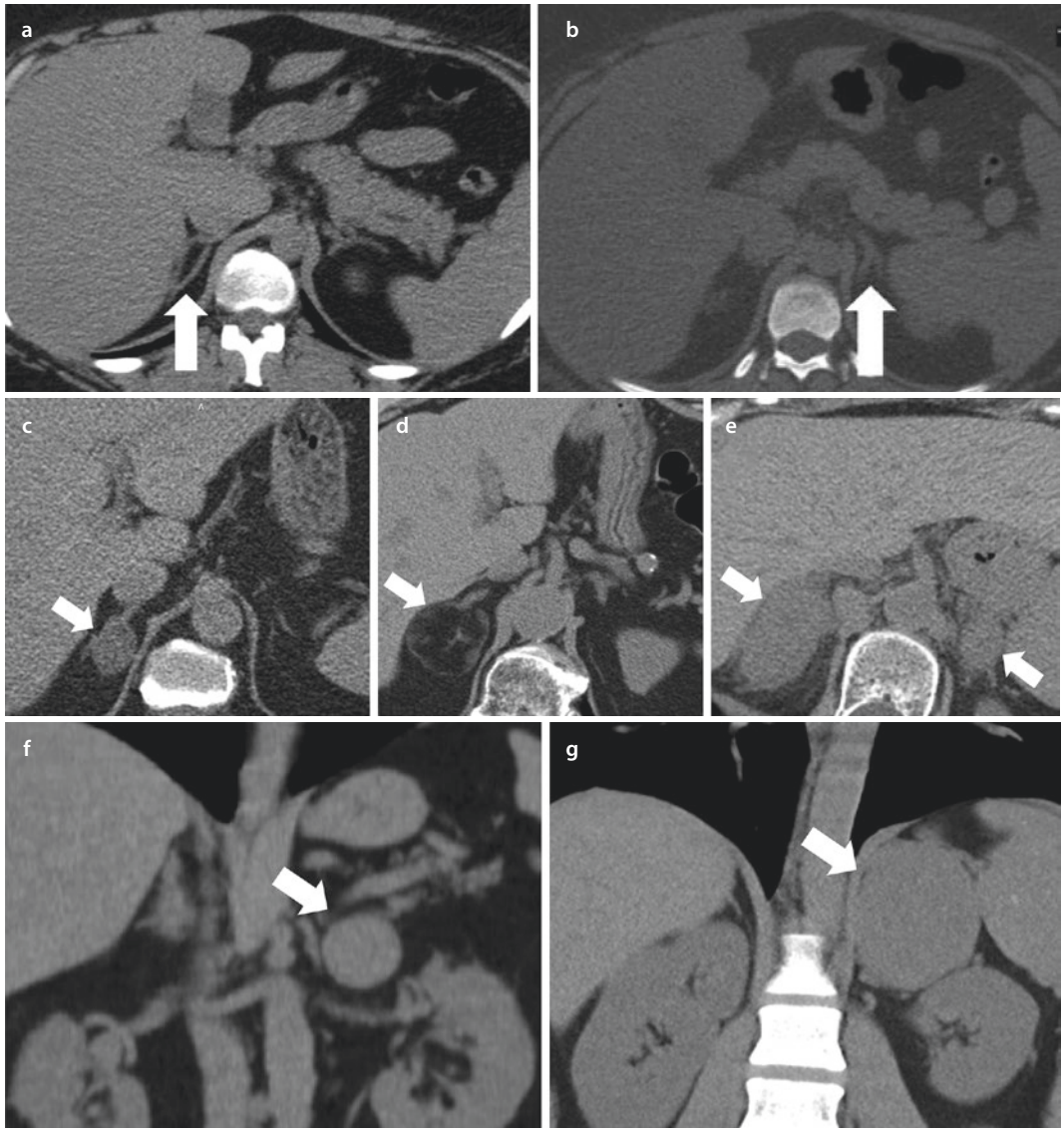

Fig. 26.2 Unenhanced CT images: **a** Normal right adrenal gland; **b** normal left adrenal gland; **c** lipid-rich adenoma (right, 2.4 cm, HU = 2); **d** myelolipoma (right, 3.2 cm, HU = -87); **e** bilateral adrenal metastases (right, 4 cm, HU = 33; left, 2.3 cm, HU 29); **f** pheochromocytoma (left, 4.2 cm, HU = 28); **g** adrenocortical carcinoma (left, 7 cm, HU = 37)

definition for loss of signal intensity. In addition, as chemical shift analysis is based on fat content in the adrenal mass, it has a limited additional diagnostic value over unenhanced CT. *^{18}F-Fluorodeoxyglucose positron emission computed tomography (^{18}FDG-PET-CT)* measures the metabolic activity of the tumor cells based on the uptake of deoxyglucose (compared to the liver). A low or no uptake is suggestive of a benign adrenal mass. However, a higher uptake is not specific for malignancy and can be seen in certain benign conditions with increased metabolic activity (hormonally active adenoma, infections). Additionally, certain malignant lesions, such as small adrenal metastasis, or a low-grade lymphoma may show low or no uptake. Other disadvantages of an ^{18}FDG-PET-CT are the limited availability and higher cost.

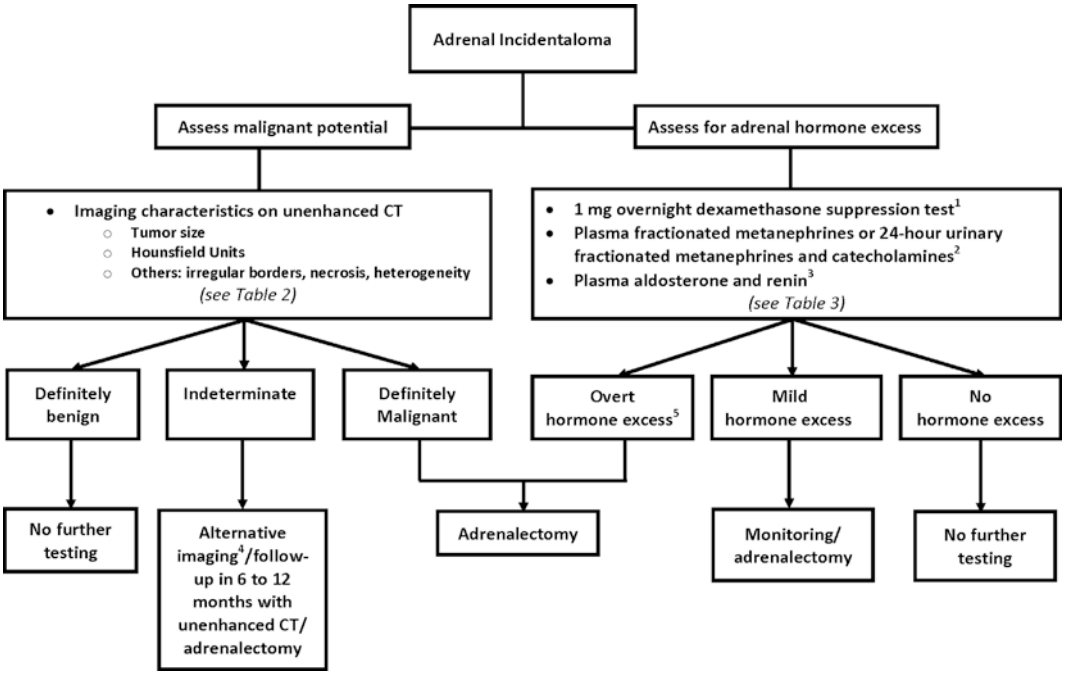

Fig. 26.3 Flowchart: Evaluation of adrenal incidentaloma. Footnote: 1. Everyone with an adrenal incidentaloma should be tested. 2. Only for patients with unenhanced attenuation >10 Hounsfield units on computed tomography. 3. Only if hypertension or unexplained hypokalemia. 4. Alternative imaging includes CT contrast washout time, MRI, or FDG-PET scan. 5. See sections on Cushing's syndrome, primary aldosteronism, and pheochromocytoma

Table 26.2 Diagnosis of a malignant adrenal mass

Variable	Cutoff	Prevalence of malignancy	Comments
Tumor size	>4 cm	30–35%	Tumor size as a predictor for malignancy needs to be considered in combination with imaging characteristics
	2–4 cm	9%	
	<2 cm	3%	
Computed tomography Unenhanced Hounsfield unit (HU)	<10 HU	0%	High level of evidence
	10–20 HU	3–5%	
	>20 HU	20–30%	
MRI chemical shift	Present	<1–5% depending on definition of chemical shift	Low evidence
	Absent	20–30%	
^{18}FDG-PET-CT scan	Positive uptake	85%	Also positive in pheochromocytomas
	Negative uptake	5–15%	Possible false-negative results in small metastases

(continued)

Table 26.2 (continued)

Variable	Cutoff	Prevalence of malignancy	Comments
Tumor growth	>1 cm in 3–6 months	Worrisome for malignancy	Also observed in adrenal hemorrhage
	0–1 cm in >6 months	Unlikely malignancy	Note that low-grade adrenocortical carcinomas may have a slow tumor growth
Serum and urine steroid metabolomics	Positive	>70% likelihood of adrenocortical carcinoma	Note that all other adrenal malignancies will have a negative result
	Negative	5% likelihood of adrenocortical carcinoma	
Adrenal biopsy	Cytology	Not accurate in adrenocortical carcinoma or adenoma >90% diagnostic accuracy in adrenal metastases	Consider non-diagnostic rate, complication rates Always exclude pheochromocytoma before biopsy Do not perform in adrenocortical neoplasms

Back to our patient

Our patient presents with an incidentally discovered indeterminate adrenal mass. Unenhanced HU of 23 cannot exclude malignancy. At this time, differential diagnosis includes a lipid-poor adrenocortical adenoma and less likely adrenocortical carcinoma and pheochromocytoma. Adrenal metastasis is possible, but is unlikely given that the patient has no history of extra-adrenal malignancy.

Is it hormonally active?

It is essential that all patients with adrenal mass undergo a thorough clinical assessment for symptoms and signs of adrenal hormone excess. Regardless of symptoms, all patients should undergo assessment with the overnight 1 mg dexamethasone suppression test (▶ Chaps. 3 and 27). Workup for primary aldosteronism is recommended only for patients with hypertension, with or without hypokalemia. Workup for catecholamine excess should be performed in anyone with indeterminate adrenal mass (Fig. 26.3). Additional workup may be necessary if initial tests are abnormal (Table 26.3).

Autonomous cortisol secretion

It is the most common etiology behind hormonally active incidentalomas. Afflicted patients can present with either overt hypercortisolism (<1–5%) or a mild autonomous cortisol secretion (MACS) that can be seen in up to 50% of AI. Patients with MACS do not possess the typical clinical features (moon-like faces, buffalo hump, centripetal obesity, easy bruising) seen in overt Cushing's syndrome. These patients usually manifest with comorbidities such as type 2 diabetes mellitus, hypertension, dyslipidemia, obesity, and/or osteoporosis.

All AIs should undergo evaluation for cortisol excess with 1 mg overnight dexamethasone suppression test (DST) followed by measurement of serum cortisol levels the next morning at 8 AM. Post-DST serum cortisol levels ≤1.8 μg/dL (≤ 50 nmol/L) exclude hypercortisolism. In patients without overt clinical features of hypercortisolism, serum cortisol values between 1.9 and 5 μg/dL (51 nmol/l to 137 nmol/l) are considered "possible mild autonomous cortisol secretion," and values >5 μg/dL (>138 nmol/L) are defined as "mild autonomous cortisol secretion." Following biochemical evidence of cor-

Table 26.3 Hormonal workup in patients with adrenal tumors

Adrenal hormone excess	Indication for testing	First-line testing	Second-line or confirmatory testing	Final diagnostic considerations
Adrenal hypercortisolism	Anyone with adrenal mass, regardless of symptoms	1 mg dexamethasone suppression test (abnormal >1.8 μg/dl)	ACTH, DHEAS 24 h urine cortisol Repeat 1 mg or perform 8 mg (high dose) dexamethasone suppression test	Patients with autonomous cortisol secretion will have abnormal dexamethasone suppression test, low ACTH, and DHEAS. 24 h urine cortisol is usually normal in mild autonomous cortisol secretion
Primary aldosteronism	Anyone with hypertension with or without spontaneous hypokalemia	Morning aldosterone and renin or renin plasma activity (abnormal aldosterone >10 ng/dL and suppressed renin)	Unnecessary if positive first-line test and hypokalemia Otherwise: salt loading test, saline infusion test, captopril challenge, or fludrocortisone test	Patients with confirmed primary aldosteronism will need subtype evaluation with imaging and adrenal vein sampling in order to proceed with adrenalectomy
Catecholamine excess	Anyone with indeterminate adrenal mass (HU > 10)	Plasma or urine metanephrines	Usually not needed unless interfering medications are suspected	Patients with suspected pheochromocytoma, extra-adrenal disease, and associated genetic predisposition need to be considered

ACTH adrenocorticotrophic hormone, *DHEAS* dehydroepiandrosterone sulfate

tisol excess, plasma adrenocorticotrophic hormone (ACTH) levels should be measured to help differentiate the etiology (ACTH vs non-ACTH dependent). Measurement of dehydroepiandrosterone sulfate (DHEAS) can be further helpful in diagnosing MACS (Table 26.3). See more in the Cushing's syndrome chapter (▶ Chap. 27).

Primary aldosteronism

In the presence of hypertension with or without unexplained hypokalemia, a morning plasma aldosterone concentration and plasma renin activity or direct renin measurements should be obtained. Positive case detection test is considered when aldosterone is >10 ng/dL and renin is suppressed (Table 26.3). Further workup may be needed, and subtype evaluation should be next performed. See more in the primary aldosteronism chapter (▶ Chap. 28).

Catecholamine excess

Around 60% of pheochromocytomas are diagnosed as incidentalomas, and only around 30% are diagnosed based on symptoms of catecholamine excess. Most patients with pheochromocytoma do not present with the classic triad of palpitations, headache, and diaphoresis, and approximately 15% are normotensive at the time of initial evaluation. As recently demonstrated by a large multicenter study, as well as a systematic review and meta-analysis, pheochromocytomas always present with unenhanced HU >10 on CT. Thus, workup for catecholamine excess is

not needed in any lipid-rich lesions with HU <10. However, as most pheochromocytomas do not present with specific symptoms, and missing a pheochromocytoma can be dangerous, workup for catecholamine excess is needed in all adrenal tumors with HU >10, regardless of size. The initial test includes either plasma fractionated metanephrines or 24 h urine for catecholamines and fractionated metanephrines (◘ Table 26.3). See more in the pheochromocytoma chapter (▶ Chap. 37).

Additional Testing

Steroid metabolomics: Measurement of steroid precursors and androgen is not routinely performed except when clinical features of hirsutism or virilization are present or imaging characteristics concerning for adrenocortical carcinoma are present. Measurement of 17-OH progesterone, 17-OH pregnenolone, and 11-deoxycortisol can be considered in patients suspected to have adrenocortical carcinoma. In addition, measurement of androgens (DHEAS, androstenedione, testosterone) frequently reveals androgen co-secretion in patients with adrenocortical carcinoma and can aid in initial diagnosis, as androgen production from a benign adrenal adenoma is exceedingly rare. Urine steroid profiling has recently been shown to have high accuracy in diagnosing adrenocortical carcinoma and may be integrated in clinical care in the future, though currently is available only in subspecialized laboratories.

Is there a role for adrenal biopsy in the management of adrenal tumors?

Adrenal biopsy is rarely needed in the diagnostic workup of adrenal tumors. Non-diagnostic rate of adrenal biopsies is around 5%, and complication rate is around 2.5%. Adrenal biopsy has poor accuracy in differentiating adrenocortical adenoma from adrenocortical carcinoma and carries a potential risk of tumor dissemination. Adrenal biopsy does have a role in patients suspected to have an adrenal metastasis or lymphoma, in which situation, diagnostic accuracy is high, and the results of biopsy may change patient's management. Adrenal biopsy should never be performed in a patient with potential pheochromocytoma and should be avoided in any potential adrenocortical carcinoma. Based on 2016 European Society for Endocrinology (ESE) guidelines, adrenal biopsy is only recommended if all of the following criteria are fulfilled: (i) the lesion is hormonally inactive (in particular, pheochromocytoma has been excluded), (ii) the lesion has not been conclusively characterized as benign by imaging, and (iii) management would be altered by knowledge of the histology.

Back to our patient

In our patient, workup for primary aldosteronism and catecholamine excess was negative. However, after the overnight 1 mg dexamethasone suppression test, the morning serum cortisol levels were elevated to 9.2 μg/dL or 253.83 nmol/L (reference range < 1.8 μg/dL or 50 nmol/L). Additional testing included morning plasma ACTH levels low at 8 pg/mL (reference range 7.6 to 60 pg/mL) and low DHEAS of 17 μg/dL (normal 15–137 μg/dL). In the absence of overt clinical features of hypercortisolism, she was diagnosed with MACS.

Given the imaging and hormonal work up, what is the most likely etiology of adrenal mass in our patient?

Finding MACS in our patient with incidentally discovered adrenal mass suggests a cortical lesion, such as adrenocortical adenoma or carcinoma. Imaging characteristics of the mass are not able to confidently exclude adrenocortical carcinoma (3.7 cm adrenal mass, HU of 23); however, as most adrenocortical carcinomas are larger, the adrenal mass is less likely to be malignant and more likely to be lipid-poor adenoma. In addition, we found that DHEAS is low, suggestive of absence of androgen co-secretion pathognomonic for adrenocortical carcinoma. Purely cortisol-secreting adrenocortical carcinomas can occur, and thus malignancy cannot be completely excluded.

What are the management options for indeterminate adrenal tumors?

In any patient with an indeterminate adrenal mass, there are three options for management: (1) adrenalectomy, (2) additional characterization of adrenal mass by another imaging test, and (3) monitoring for tumor growth (Fig. 26.3). Choosing a particular option depends on the degree of suspicion for malignancy, availability of surgical expertise or advanced imaging, and patient's preference. *Adrenalectomy* is a logical choice in patients with an adrenal mass highly likely to be malignant (large adrenal mass, necrosis, heterogeneity) and/or presence of adrenal hormone excess. Open adrenalectomy is performed for adrenal tumors likely to be malignant, and laparoscopic adrenalectomy is the procedure of choice for benign adrenal adenomas. *Additional imaging* (contrast washout, MRI, ^{18}FDG-PET-CT) can characterize the adrenal mass in more detail. For example, proceeding with ^{18}FDG PET-CT scan in a patient with an indeterminate adrenal mass on unenhanced CT scan will characterize the metabolic activity of the adrenal mass and may help decide on a more aggressive approach (if positive ^{18}FDG uptake) or conservative approach (if negative ^{18}FDG uptake). Finally, in patients with smaller indeterminate adrenal tumors likely to be lipid-poor adenoma, *re-imaging in 6–12 months to examine tumor growth* will help confirm the benign etiology (if no growth). Alternatively, reviewing past imaging can provide information on tumor growth.

What are the management options for MACS?

Once the diagnosis of MACS is made, patients should be screened for type 2 diabetes mellitus, hypertension, and asymptomatic vertebral fractures. It is important to note that the risk of MACS progressing to overt hypercortisolism is extremely low (<0.5%). Depending on the degree of cortisol excess and presence of comorbidities, adrenalectomy could be considered. Previous studies reported that adrenalectomy in MACS may lead to improvement of hypertension, diabetes mellitus, dyslipidemia, obesity, and bone health. However, the degree of improvement is variable, and identifying patients most likely to benefit from adrenalectomy is challenging. Thus, option of adrenalectomy versus conservative approach needs to be discussed with each patient. Presence of MACS-associated comorbidities, imaging phenotype, and patient's preference are the individual factors that play a role in the final decision.

Back to our patient

Our patient has hypertension, diabetes mellitus type 2, and obesity. On further workup, she was also found to have dyslipidemia. Bone density revealed osteopenia, with a T-score of −1.8 (▶ Chap. 24). Spine X-ray did not reveal any asymptomatic vertebral fractures. After discussing options for management, patient and endocrinologist decided on adrenalectomy for management of MACS. Reasons for this choice were (1) confirmed high degree of autonomous cortisol secretion (post-DST cortisol >5 μ/dL, low ACTH, and DHEAS), (2) presence of comorbidities possibly related to long-standing MACS, (3) indeterminate imaging phenotype of adrenal mass, and (4) patient's preference. Following this decision, patient had laparoscopic adrenalectomy by an experienced adrenal surgeon. Pathology confirmed adrenocortical adenoma. Patient was initiated on hydrocortisone therapy for postoperative adrenal insufficiency. Recovery of hypothalamic-pituitary-adrenal axis occurred 7 months later, confirmed by hormonal workup, and hydrocortisone was discontinued. At 12 months follow-up, patient continued to have hypertension but required a lower dose of lisinopril. Diabetes mellitus type 2 was better controlled allowing discontinuation of glipizide. Patient lost 5 kg during 3 months post-adrenalectomy. She continues to have stable osteopenia on repeat bone density.

What is the recommended follow up in patients with confirmed non-functioning adrenocortical adenomas?

In a patient with a clearly benign (HU < 10) nonfunctioning adrenal adenoma, further monitoring with imaging or repeated hormonal workup is not needed. As reported in a recent meta-analysis of 32 studies including 4121 patients, 4% of adrenal adenoma demonstrated a growth of at least 1 cm over around 40 months of follow-up; however, no patient developed adrenal malignancy. In addition, <0.5% of patients with nonfunctioning adrenal adenomas or MACS developed new primary aldosteronism, overt hypercortisolism, or pheochromocytoma. Thus, there is no need to monitor patients with benign nonfunctioning adrenal adenomas. Patients with MACS not treated by adrenalectomy require monitoring for MACS-associated comorbidities so that aggressive therapy for diabetes mellitus type 2, hypertension, dyslipidemia, and osteoporosis is promptly initiated.

Tips

The reader is advised to read the following chapters on adrenal tumors: adrenal Cushing's syndrome (▶ Chap. 27), primary aldosteronism (▶ Chap. 28), adrenocortical cancer (▶ Chap. 30), and pheochromocytoma (▶ Chap. 37).

Take-Home Messages

- Adrenal incidentaloma is common, detected on 5–7% of cross-sectional imaging.
- In any patient with adrenal mass, two important questions should be addressed: (A) Is the mass benign or malignant? (B) Is the mass nonfunctioning or hormonally active?
- Unenhanced abdominal CT is the recommended initial test to assess the imaging phenotype and size of the mass.
- Homogenous adrenal masses with unenhanced CT-attenuation of <10 HU indicates lipid-rich benign adenoma, and malignancy or pheochromocytoma can be confidently excluded.
- In patients with indeterminate adrenal tumors, management options include adrenalectomy, imaging with another test (^{18}FDG PET-CT scan), or interval imaging to evaluate tumor growth.
- Adrenal biopsy is rarely recommended, usually reserved for adrenal tumors likely to be adrenal metastases (and only after excluding pheochromocytoma).
- All adrenal incidentalomas should undergo biochemical hormonal evaluation for autonomous cortisol secretion (1 mg overnight dexamethasone suppression test), regardless of symptoms. Workup for catecholamine excess (pheochromocytomas) should be done only in indeterminate adrenal tumors (HU > 10), and workup for primary aldosteronism in anyone with hypertension.
- Urine steroid metabolomics is an emerging diagnostic test for adrenocortical carcinoma.
- Any patient with autonomous cortisol secretion should be evaluated for cortisol-induced metabolic abnormalities. Decision on adrenalectomy for autonomous cortisol secretion should consider the degree of cortisol abnormality, presence of comorbidities, adrenal tumor phenotype, and patient's preference.
- No further workup or monitoring is recommended for nonfunctioning benign adrenal tumors as the risk of malignancy or new hormonal excess in these patients is <0.5%.

Suggested Reading

1. Bancos I, Alahdab F, Crowley RK, Chortis V, Delivanis DA, Erickson D, Natt N, Terzolo M, Arlt W, Young WF Jr, Murad MH. Therapy of endocrine disease: Improvement of cardiovascular risk factors after adrenalectomy in patients with adrenal tumors and subclinical Cushing's syndrome: a systematic review and meta-analysis. Eur J Endocrinol. 2016;175(6):R283–r295. https://doi.org/10.1530/eje-16-0465.
2. Bancos I, Arlt W. Diagnosis of a malignant adrenal mass: the role of urinary steroid metabolite profiling. Curr Opin Endocrinol Diabet Obesity. 2017;24(3):200–7. https://doi.org/10.1097/med.0000000000000333.
3. Bancos I, Taylor AE, Chortis V, Sitch AJ, Jenkinson C, Davidge-Pitts CJ, Lang K, Tsagarakis S, Macech M, Riester A, Deutschbein T, Pupovac ID, Kienitz T, Prete A, Papathomas TG, Gilligan LC, Bancos C, Reimondo G, Haissaguerre M, Marina L, Grytaas MA, Sajwani A, Langton K, Ivison HE, Shackleton CHL, Erickson D, Asia M, Palimeri S, Kondracka A, Spyroglou A, Ronchi CL, Simunov B, Delivanis DA, Sutcliffe RP, Tsirou I, Bednarczuk T, Reincke M, Burger-Stritt S, Feelders RA, Canu L, Haak HR, Eisenhofer G, Dennedy MC, Ueland GA, Ivovic M, Tabarin A, Terzolo M, Quinkler M, Kastelan D, Fassnacht M, Beuschlein F, Ambroziak U, Vassiliadi DA, O'Reilly MW, Young WF Jr, Biehl M, Deeks JJ, Arlt W. ENSAT EURINE-ACT Investigators. Bancos I, et al. Urine steroid metabolomics for the differential diagnosis of adrenal incidentalomas in the EURINE-ACT study: a prospective test validation study. Lancet Diabetes Endocrinol. 2020 Sep;8(9):773–781. https://doi.org/10.1016/S2213-8587(20)30218-7. Epub 2020 Jul 23. Lancet Diabetes Endocrinol. 2020. PMID: 32711725.
4. Bovio S, Cataldi A, Reimondo G, Sperone P, Novello S, Berruti A, Borasio P, Fava C, Dogliotti L, Scagliotti GV, Angeli A, Terzolo M. Prevalence of adrenal incidentaloma in a contemporary computerized tomography series. J Endocrinol Invest. 2006;29(4):298–302. https://doi.org/10.1007/bf03344099.
5. Canu L, Van Hemert JAW, Kerstens MN, Hartman RP, Khanna A, Kraljevic I, Kastelan D, Badiu C, Ambroziak U, Tabarin A, Haissaguerre M, Buitenwerf E, Visser A, Mannelli M, Arlt W, Chortis V, Bourdeau I, Gagnon N, Buchy M, Borson-Chazot F, Deutschbein T, Fassnacht M, Hubalewska-Dydejczyk A, Motyka M, Rzepka E, Casey RT, Challis BG, Quinkler M, Vroonen L, Spyroglou A, Beuschlein F, Lamas C, Young WF, Bancos I, Timmers H. CT characteristics of pheochromocytoma: relevance for the evaluation of adrenal incidentaloma. J Clin Endocrinol Metabol. 2019;104(2):312–8. https://doi.org/10.1210/jc.2018-01532.
6. Decmann A, Perge P, Tóth M, Igaz P. Adrenal myelolipoma: a comprehensive review. Endocrine. 2018;59(1):7–15. https://doi.org/10.1007/s12020-017-1473-4.
7. Delivanis DA, Erickson D, Atwell TD, Natt N, Maraka S, Schmit GD, Eiken PW, Nathan MA, Young WF Jr, Bancos I. Procedural and clinical outcomes of percutaneous adrenal biopsy in a high-risk population for adrenal malignancy. Clin Endocrinol. 2016;85(5):710–6. https://doi.org/10.1111/cen.13117.
8. Dinnes J, Bancos I, Ferrante di Ruffano L, Chortis V, Davenport C, Bayliss S, Sahdev A, Guest P, Fassnacht M, Deeks JJ, Arlt W. Management of endocrine disease: Imaging for the diagnosis of malignancy in incidentally discovered adrenal masses: a systematic review and meta-analysis. Eur J Endocrinol. 2016;175(2):R51–64. https://doi.org/10.1530/eje-16-0461.
9. Ebbehoj A, Li D, Kaur RJ, Zhang C, Singh S, Li T, Atkinson E, Achenbach S, Khosla S, Arlt W, Young WF, Rocca WA, Bancos I. Ebbehoj A, et al. Epidemiology of adrenal tumours in Olmsted County, Minnesota, USA: a population-based cohort study. Among authors: bancos i. Lancet Diabetes Endocrinol. 2020 Nov;8(11):894–902. https://doi.org/10.1016/S2213-8587(20)30314-4. Lancet Diabetes Endocrinol. 2020. PMID: 33065059
10. Elhassan YS, Alahdab F, Prete A, Delivanis DA, Khanna A, Prokop L, Murad MH, O'Reilly MW, Arlt W, Bancos I. Natural history of adrenal incidentalomas with and without mild autonomous cortisol excess: a systematic review and meta-analysis. Ann Intern Med. 2019;171(2):107–16. https://doi.org/10.7326/m18-3630.
11. Fassnacht M, Arlt W, Bancos I, Dralle H, Newell-Price J, Sahdev A, Tabarin A, Terzolo M, Tsagarakis S, Dekkers OM. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2016;175(2):G1–g34. https://doi.org/10.1530/eje-16-0467.
12. Hamidi O, Raman R, Lazik N, Iniguez-Ariza N, McKenzie TJ, Lyden ML, Thompson GB, Dy BM, Young WF Jr, Bancos I. Clinical course of adrenal myelolipoma: a long-term longitudinal follow-up study. Clin Endocrinol. 2020;93(1):11–8. https://doi.org/10.1111/cen.14188.
13. Iñiguez-Ariza NM, Kohlenberg JD, Delivanis DA, Hartman RP, Dean DS, Thomas MA, Shah MZ, Herndon J, McKenzie TJ, Arlt W, Young WF Jr, Bancos I. Clinical, biochemical, and radiological characteristics of a single-center retrospective cohort of 705 large adrenal tumors. Mayo Clin Proc Innov Quality Outcomes. 2018;2(1):30–9. https://doi.org/10.1016/j.mayocpiqo.2017.11.002.
14. Mao JJ, Dages KN, Suresh M, Bancos I. Presentation, disease progression, and outcomes of adrenal gland metastases. Clin Endocrinol. 2020; https://doi.org/10.1111/cen.14268.
15. Vaidya A, Hamrahian A, Bancos I, Fleseriu M, Ghayee HK. The evaluation of incidentally discovered adrenal masses. Endocr Pract. 2019;25(2):178–92. https://doi.org/10.4158/dscr-2018-0565.

Adrenal Cushing's Syndrome

Peter Igaz

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_27

Opening

In this chapter, the reader will get acquainted with the clinical features, diagnosis, and treatment of cortisol overproduction (Cushing's syndrome) related to adrenal tumors. The pituitary and ectopic forms are discussed in different chapters (► Chaps. 3 and 45).

27

Definition of the Disease

Cushing's syndrome is related to the overproduction of cortisol (hypercortisolism). The most common form of Cushing's syndrome is exogenous (iatrogenic) that is associated with the widespread use of steroids in the treatment of various autoimmune and oncologic diseases. Endogenous Cushing's syndrome can be classified as ACTH-dependent or ACTH-independent. ACTH-dependent forms include pituitary ACTH-producing adenoma (Cushing's disease) and ectopic ACTH syndrome that are discussed in other respective chapters of the book. The most common form of hypercortisolism is Cushing's disease representing 60–70% of all endogenous hypercortisolism, but it is still very rare with an incidence varying between 1 and 7/million/year in various studies. Adrenal and ectopic ACTH-related forms of Cushing are both responsible for 15–20% of all Cushing's syndrome, respectively. ACTH-independent Cushing's syndrome is invariably associated with adrenal tumors, mostly benign adrenocortical adenoma and rarely adrenocortical cancer (discussed in ► Chap. 30).

Due to the widespread activities of cortisol in the human body, its overproduction is related to dysfunctions of several organ systems including metabolic, musculoskeletal, immune, and neuropsychiatric complications among others.

Case Presentation

A 30-year-old woman was admitted to our endocrine consultation. Her case history includes hypertension known for 5 years and diabetes mellitus treated with metformin for 3 years. She had an epileptic attack 2 years ago due to an ischemic stroke, and later she had pulmonary embolization. Factor V Leiden mutation heterozygosity has been established, and for 2 years, she receives anticoagulation with rivaroxaban. She had right pleuropneumonia 8 months ago. She is known to have major depression for 2 years and tried to commit suicide on two occasions (the last occurred 2 months before her current admission with benzodiazepine overdose). Ophthalmological examination revealed cataract on both lenses, and 2 months ago, glaucoma has also been described.

She had a weight gain of 20 kgs in the past 1–1.5 years. Her menstrual cycle became irregular in the past months. She complains about cognitive impairment, particularly regarding short-term memory.

What are the features from this case that are suspicious for hypercortisolism (Cushing's syndrome)?

The patient complained of weight gain. By physical examination, centripetal obesity with thin limbs, moon-like face, pronounced abdominal obesity (Fig. 27.1a), and a buffalo hump (Fig. 27.1b) was evident along with typical striae of the belly (Fig. 27.1a).

The major clinical symptoms associated with Cushing's syndrome are presented in Table 27.1. This case presents almost all important features of Cushing's syndrome including hypertension, diabetes mellitus, and increased risk for infection (pleuropneumonia 8 months before admission). Ophthalmologic complications including cataracts and increased intraocular pressure (glaucoma) are mostly seen with severe exogenous Cushing's syndrome, but she has presented these. As cortisol suppresses pituitary gonadotropin secretion, menstrual irregularities and sexual dysfunction are also common in Cushing's syndrome.

A major point in her history is related to the major depression that even led to suicide attempts. Psychiatric complications are common in Cushing's syndrome.

The patient was found to be heterozygous for a factor V. Leiden mutation. Is this relevant for the diagnosis of Cushing's syndrome?

The increased risk for thromboembolic events is being regarded as an important feature of Cushing's syndrome. The combination of a Factor V Leiden mutation heterozygosity and hypercortisolism could have contributed to the repeated thromboembolic episodes of her case history.

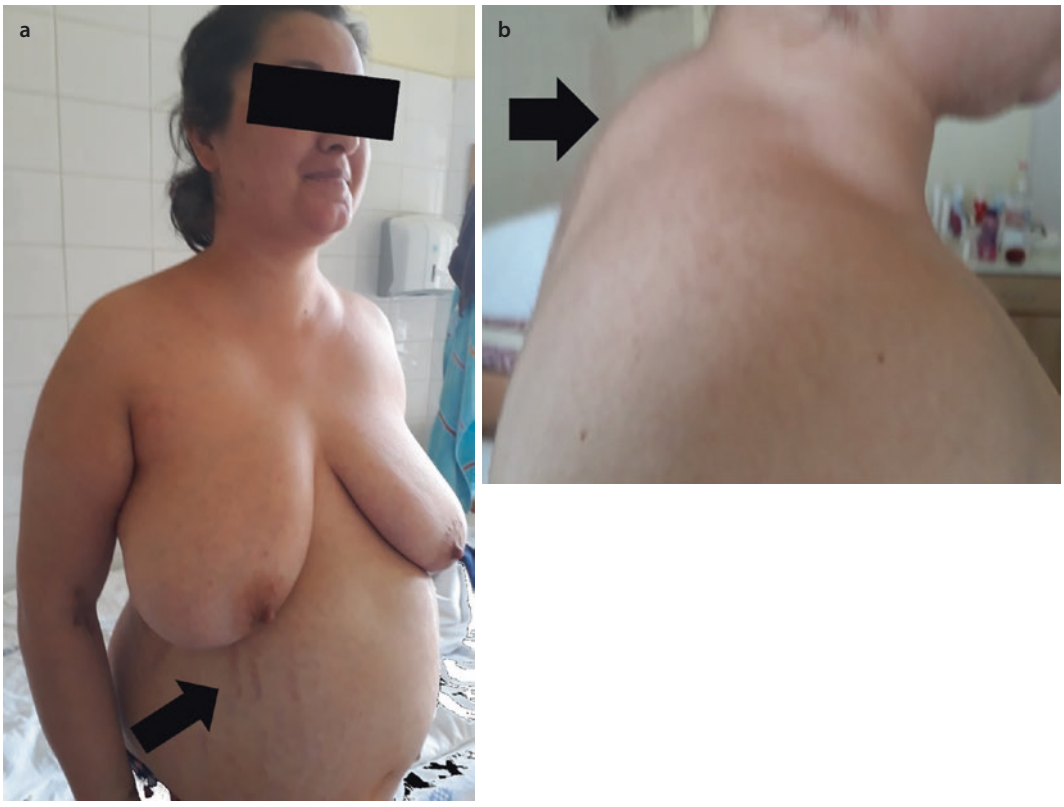

Fig. 27.1 **a** Centripetal obesity, moon-like face, and abdominal striae (arrow). **b** buffalo hump

Table 27.1 Major clinical features of Cushing's syndrome

Fat distribution changes	Centripetal obesity Moon-like face Buffalo hump
Metabolic changes	Diabetes mellitus or impaired glucose tolerance
Musculoskeletal	Muscle weakness Osteoporosis
Cardiovascular	Hypertension Frequent thromboembolic events
Skin	Striae (mostly on the abdomen and axilla Impaired wound healing Hyperpigmentation in ACTH-dependent forms
Immune	Increased susceptibility to infections
Eye	Cataract, glaucoma
Reproductive functions	Menstrual irregularities (secondary amenorrhea) Decreased libido
Neuropsychiatric disorders	Cognitive impairment Mood changes Depression Psychosis

Regarding the possibility of bone loss, what kind of examination should be performed?

Osteodensitometry should be performed that showed a T-score of −1.6 at the lumbar spine and − 0.6 at the left femoral neck. (T-score represents the standard deviation (SD) of bone density from the average healthy population.) As T-score was between −1 and − 2.5 at the lumbar spine, her condition should be regarded as **osteopenia**. (Osteoporosis is defined as a T-score below −2.5. More details on this issue can be found in the chapter on osteoporosis (▶ Chap. 24).)

Is it possible to differentiate the various forms of endogenous Cushing's syndrome based on clinical symptoms?

No, hormonal tests and later imaging are needed for their differentiation. There are, however, some clues that might argue for certain forms. For example, hypokalemia is mostly seen with excessive cortisol secretion as in these cases, the capacity of the HSD11B2 enzyme (11ß-hydroxysteroid dehydrogenase 2) that defends the aldosterone receptor from cortisol action is exhausted, and cortisol can then bind the aldosterone receptor and thus produce mineralocorticoid effects. Excessive cortisol secretion is mostly seen in Cushing's syndrome associated with ectopic ACTH syndrome or adrenocortical cancer.

Hirsutism (pathological hair overgrowth in androgen-dependent regions in women, e.g., face, breast, back, abdomen, thighs) is more common in ACTH-driven forms than in benign adrenocortical adenoma-related Cushing's syndrome, as in the latter, the low ACTH prevents adrenal androgen secretion. In contrast, severe hirsutism and virilization might occur in adrenocortical cancer-secreting androgens.

Which hormone tests can be used for screening Cushing's syndrome?

Although the clinical picture seems to be clear-cut, as with every disease in endocrinology, we need hormonal evidence. When screening patients with suspicion for Cushing's syndrome, three major test types can be performed:

(i) 24-hour urinary free cortisol
(ii) Low-dose dexamethasone suppression test
(iii) Examination of the circadian cortisol rhythm by late night (around midnight) cortisol measurement (from blood or saliva)

In patients with a high degree of suspicion for hypercortisolism, two or three tests should be performed. When screening patients who are unlikely to have Cushing's syndrome, the low-dose dexamethasone suppression test is usually enough to carry out.

Urinary free cortisol was elevated: 820.8 nmol/l (normal range 100.0–379.0). By low-dose (usually overnight) dexamethasone suppression test, the exogenous glucocorticoid dexamethasone suppresses pituitary adrenocorticotropin (ACTH) secretion and thereby in normal individuals suppresses cortisol the next morning below 50 nmol/l (1.8 µg/dl). Dexamethasone is used as a synthetic glucocorticoid in this test, as it does not give cross reactivity with cortisol in the laboratory measurements.

Morning cortisol after overnight 1 mg dexamethasone was 319.6 nmol/l (normal <50 nmol/l).

Regarding the circadian rhythm, normally, cortisol has its nadir at midnight and rises sharply at dawn before waking up. Elevated late night cortisol is also a sensitive marker of hypercortisolism.

Late night cortisol from saliva was 17.460 nmol/l (normal <11.900) and from blood 556.30 nmol/l (normal<136.00), both significantly elevated.

Salivary cortisol is also free cortisol, similar to that of urine, whereas in the blood, cortisol is bound by cortisol-binding globulin (CGB) and, thus, affected by changes in CGB concentration (like in pregnancy and anticoncipient use as estrogens increase CBG levels). Therefore in pregnancy and in women taking oral anticoncipients, total cortisol levels cannot be interpreted without suitable reference ranges.

Hormonal examination should not be performed in women taking oral contraceptives, only after stopping these for 3 months in general.

An advantage of salivary cortisol over blood cortisol is that it can be sampled by the patient herself and no in-patient setting is needed.

Is there a bone marker that could be indicative of active Cushing's syndrome?

Yes, as osteocalcin is a measurement of bone buildup, low osteocalcin levels are found in active hypercortisolism. Serum osteocalcin of the patient was 2.76 ng/mL (normal range: 12.00–41.00).

How should we proceed?

We have now the hormonal diagnosis of Cushing's syndrome, but we don't know its origin, whether it is an ACTH-dependent or ACTH-independent form.

Next, an ACTH measurement is performed that showed 1 pg/mL (normal 5–60 pg/ml); thus it is an ACTH-independent, adrenal form.

Dehydroepiandrosterone sulphate (DHEAS) was low (0.75 µmol/L – normal range 1.65-11.00). What can be the explanation?

DHEAS is a steroid hormone produced by the adrenal cortex, a weak androgen hormone that is in fact produced in the largest amount from all steroid hormones. (Its physiological function is, however, still unclear, but there are some data showing benefit when substituting it in patients with Addison's disease – see corresponding ► Chap. 31) As it is also ACTH-driven, the low ACTH due to cortisol overproduction results in low DHEAS. In contrast, in ACTH-dependent Cushing's syndrome forms, DHEAS is usually elevated.

If the patient had high DHEAS levels and an adrenal tumor, what can be thought of?

Overproduction of DHEAS and other adrenal androgens can be a feature of adrenocortical cancer. Novel molecular approaches using urinary steroid hormone metabolomics show that even clinically silent adrenocortical cancer secrete steroids, mostly androgen precursors.

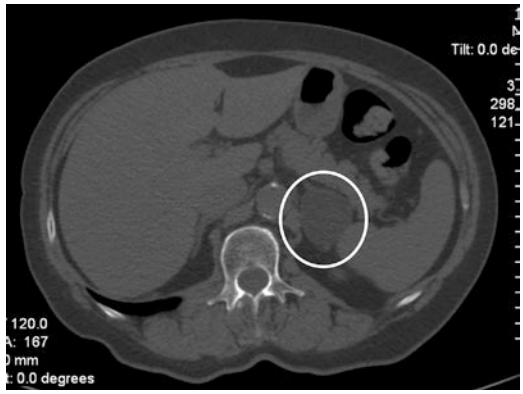

Fig. 27.2 CT scan showing a left adrenal tumor that is hypodense in comparison with the liver. The tumor is homogeneous, encapsulated. No signs of malignancy

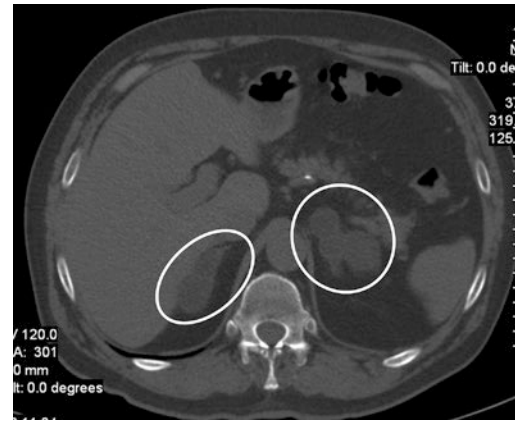

Fig. 27.3 CT scan of a bilateral macronodular adrenal hyperplasia (BMAH). Note the large nodules especially in the left adrenal

How should the adrenal tumor be identified?

Computed tomography (CT) and magnetic resonance imaging (MRI) are the modalities proposed for the study of the adrenals.

CT showed a left adrenal tumor with low density characteristic for fat (Fig. 27.2).

Are there bilateral forms of primary benign adrenal disease leading to Cushing's syndrome?

Yes. Two forms of ACTH-independent bilateral adrenal hyperplasia are important to mention. Micronodular adrenal hyperplasia (otherwise called primary pigmented nodular adrenal hyperplasia (PPNAD)) is mostly associated with Carney complex. (Carney complex is a very rare, autosomal dominantly inherited multiple endocrine neoplasia syndrome which includes spotty skin pigmentation, endocrine tumors (e.g., PPNAD, large cell calcifying Sertoli cell tumors of the testes, thyroid tumors, ovarian cysts), and non-endocrine tumors, e.g., cardiac myxoma. A part of Carney complex cases is caused by mutations of the protein kinase A regulatory subunit.)

In bilateral macronodular adrenal hyperplasia (BMAH), both adrenals are enlarged and harbor nodules usually larger than 10 mm (Fig. 27.3). BMAH is often related to ectopic hormone receptor expression (e.g., β-adrenergic receptors, vasopressin, or luteinizing hormone). Cushing's syndrome is usually mild, and often subclinical Cushing's syndrome is observed. Novel findings have showed mutations in the gene *ARMC5* (Armadillo repeat containing 5, a putative tumor suppressor) in some forms of BMAH.

What kind of treatment options can be envisaged in the patient's case?

The primary treatment is surgical. If the Cushing's syndrome is so severe that the symptoms of hypercortisolism should be rapidly alleviated (that is mostly not the case for adrenal adenoma-associated Cushing's syndrome) or very rarely if the patient is no candidate for surgery or declines it, steroid biosynthesis inhibitors can be introduced. Surgery for tumors with benign appearance (high fat content, >50% contrast washout by CT) is usually performed by laparoscopy.

What kind of steroid biosynthesis inhibitors can be used?

Metyrapone, an inhibitor of the enzyme 11β-hydroxylase 1 (CYP11B1), catalyzing the last step in cortisol biosynthesis, can

be given, and it has a relatively fast action. Its main side effects include hirsutism and water retention as the reduction in cortisol leads to elevated ACTH stimulating adrenal androgen and to a lesser extent mineralocorticoid release. Ketoconazole (originally an antimycotic drug) inhibits several steroid biosynthetic enzymes and is a good option for chronic treatment, but liver functions should be regularly monitored because of its liver toxicity. Mitotane is intended for use in adrenocortical cancer patients as an adrenolytic drug also having inhibitory effects on steroid biosynthetic enzymes (see corresponding chapter on adrenocortical cancer).

Which steroid biosynthesis inhibitor can be given intravenously?

Etomidate (originally an anesthetic drug) can be given via intravenous infusion, and it is the fastest acting steroid inhibitory drug. It can only be given in the intensive care unit.

What kind of complications can be expected postoperatively, and how should these be prevented?

The most important complication is related to the suppression of the contralateral normal adrenal cortex due to low ACTH levels. The normal adrenal can be atrophized, and it can take several weeks or months for it to recover. Steroid replacement with hydrocortisone should be started postoperatively with a higher dose in the beginning (e.g., starting with 50 mg a day on the first day postoperatively, and this should be gradually tapered to a daily maintenance dose of 20–30, than 15–20 mg).

If the substitution dose is insufficient, patients often complain about weakness, low blood pressure, and muscle and joint pains.

Do patients need mineralocorticoid substitution, as well?

No, as ACTH does not have a major role in the regulation of aldosterone secretion (that is mainly regulated by serum potassium and angiotensin II); thus there is no aldosterone deficiency to be expected.

How can we judge whether the normal adrenal gland has recovered?

This should be based mainly on clinical status. The normalization of ACTH can be a marker. A short ACTH stimulation test can also be performed (250 μg tetracosactide; if cortisol goes over 540 nmol/l (20 μ/dl) after 60 min of injection, it is a normal response).

What is subclinical Cushing's syndrome?

In many patients with adrenal tumors, no overt Cushing's syndrome can be seen, but hormonal tests can be in part positive, e.g., no full suppression by the overnight 1 mg dexamethasone suppression test (cortisol >50 nmol/l) or increased urinary free cortisol secretion. The patients can present some features related to cortisol overproduction, e.g., diabetes mellitus, hypertension, or obesity, and there are some studies showing (but it is not universally accepted) that adrenalectomy can improve these patients.

Are there special features of treatment of ACTH-independent adrenal hyperplasia?

Bilateral adrenalectomy is indicated for both micro- and macronodular adrenal hyperplasia leading to overt hypercortisolism. In BMAH related to moderately active Cushing's syndrome, unilateral adrenalectomy might also be advantageous. If the pathogenic role of ectopic hormone receptor activity can be confirmed in BMAH (e.g., by hormonal tests), some pharmacological approaches (e.g., β-adrenergic receptor blocker or gonadotropin-releasing hormone (GnRH) agonist suppressing LH production depending on the receptor expression can be tried).

Tips

- The reader is advised to read (or repeat) the chapters on pituitary Cushing's disease (▶ Chap. 3), ectopic ACTH syndrome (▶ Chap. 45), and adrenocortical cancer (▶ Chap. 30).

27

Take-Home Messages

- Adrenal Cushing's syndrome is a rare disease leading to serious morbidity.
- The suspicion for the disease can be raised based on the characteristic clinical symptoms, but hormonal diagnosis is always needed to confirm the disease.
- Adrenal Cushing's syndrome is associated with low ACTH (adrenocorticotropin) levels, as it is an ACTH-independent form of the disease.
- Computed tomography and magnetic resonance imaging are necessary for finding the tumor.
- Treatment is primarily surgical (usually laparoscopic).
- If the patient is not eligible for surgery, or pretreatment for severe Cushing's syndrome is needed before surgery, steroid biosynthesis inhibitors can be given.
- Due to the suppression of the contralateral normal adrenal gland, patients usually need steroid substitution after surgery for some months. The dose of hydrocortisone should be tapered based on clinical symptoms.

Suggested Reading

1. Bertagna X. Management of endocrine disease: can we cure Cushing's disease? A personal view. Eur J Endocrinol. 2018;178(5):R183–r200. https://doi.org/10.1530/eje-18-0062.
2. De Venanzi A, Alencar GA, Bourdeau I, Fragoso MC, Lacroix A. Primary bilateral macronodular adrenal hyperplasia. Curr Opin Endocrinol Diabetes Obesity. 2014;21(3):177–84. https://doi.org/10.1097/med.0000000000000061.
3. Espiard S, Drougat L, Libe R, Assie G, Perlemoine K, Guignat L, Barrande G, Brucker-Davis F, Doullay F, Lopez S, Sonnet E, Torremocha F, Pinsard D, Chabbert-Buffet N, Raffin-Sanson ML, Groussin L, Borson-Chazot F, Coste J, Bertagna X, Stratakis CA, Beuschlein F, Ragazzon B, Bertherat J. ARMC5 mutations in a large cohort of primary macronodular adrenal hyperplasia: clinical and functional consequences. J Clin Endocrinol Metabol. 2015;100(6):E926–35. https://doi.org/10.1210/jc.2014-4204.
4. Igaz P, Tombol Z, Szabo PM, Liko I, Racz K. Steroid biosynthesis inhibitors in the therapy of hypercortisolism: theory and practice. Curr Med Chem. 2008;15(26):2734–47. https://doi.org/10.2174/092986708786242921.
5. Loriaux DL. Diagnosis and differential diagnosis of Cushing's syndrome. N Engl J Med. 2017;376(15):1451–9. https://doi.org/10.1056/NEJMra1505550.
6. Nieman LK. Diagnosis of Cushing's syndrome in the modern era. Endocrinol Metabol Clin North Am. 2018;47(2):259–73. https://doi.org/10.1016/j.ecl.2018.02.001.
7. Nieman LK, Biller BM, Findling JW, Murad MH, Newell-Price J, Savage MO, Tabarin A. Treatment of Cushing's syndrome: an endocrine society clinical practice guideline. J Clin Endocrinol Metabol. 2015;100(8):2807–31. https://doi.org/10.1210/jc.2015-1818.
8. Sereg M, Toke J, Patocs A, Varga I, Igaz P, Szucs N, Horanyi J, Pusztai P, Czirjak S, Glaz E, Racz K, Toth M. Diagnostic performance of salivary cortisol and serum osteocalcin measurements in patients with overt and subclinical Cushing's syndrome. Steroids. 2011;76(1–2):38–42. https://doi.org/10.1016/j.steroids.2010.08.007.
9. Wagner-Bartak NA, Baiomy A, Habra MA, Mukhi SV, Morani AC, Korivi BR, Waguespack SG, Elsayes KM. Cushing syndrome: diagnostic workup and imaging features, with clinical and pathologic correlation. Am J Roentgenol. 2017;209(1):19–32. https://doi.org/10.2214/ajr.16.17290.

Primary Aldosteronism

Teresa Maria Seccia

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_28

Opening

In this chapter, a paradigmatic case of primary aldosteronism presenting with arterial hypertension and hypokalaemia is illustrated. However, such presentation is not common, and this explains why many cases of primary aldosteronism remain undiagnosed, leaving the patients to high risk of developing organ damage and cardiovascular events. To avoid missing the diagnosis of primary aldosteronism, information on what patients are to be screened, and what tests should be performed, are provided. Then, some suggestions and tips are offered to help the reader with the interpretation of the laboratory tests that sometimes offer traps. Finally, the treatment for the unilateral and bilateral forms of primary aldosteronism, mostly aldosterone-producing adenoma and bilateral adrenal hyperplasia, is discussed.

28

Definition of the Disease

Primary aldosteronism (PA) is the most common form of endocrine hypertension, defined as a condition characterized by aldosterone production inappropriately high for the sodium status and relatively autonomous from the major regulators of aldosterone secretion, such as angiotensin II. PA is more frequent than previously believed, with a prevalence rate of 6% in the primary care setting, 11% among patients referred to the specialized centres for arterial hypertension and 30% among those with resistant hypertension. Notwithstanding the huge evidences documenting that PA is not a rare disease, a survey of general practitioners in two European countries with a high level of health care reported that physicians screened only 1–2% of their hypertensive patients.

Due to the deleterious effects of excess aldosterone on the cardiovascular system, patients with PA have a higher cardiovascular risk profile than age-, sex- and blood pressure-matched subjects with essential hypertension. Hence, the early identification of PA patients is crucial for the prevention of cardiovascular events. Once identifying the PA patients, it is fundamental to discriminate between bilateral and unilateral PA forms because the treatment is different. Bilateral forms, which include adrenal hyperplasia (also known as bilateral adrenal hyperplasia, BAH), require medical therapy, whereas the unilateral forms, mostly aldosterone-producing adenoma (APA, Conn's adenoma), should be treated with unilateral adrenalectomy.

The prevalence rates of BHA and APA differ among surveys, with BAH ranging from 50% to 70% of PA cases, depending on the strategy used for PA subtyping. The phenotype characterized by hypokalaemia and metabolic alkalosis is rare and, however, more frequent for APA. Normokalaemia is found in up to half of cases of PA.

Case Presentation

A 64-year-old man was referred to our centre for arterial hypertension by his general practitioner. His history includes hypertension known for 24 years, treated with felodipine (10 mg o.d.), hypercholesterolemia, benign prostatic hyperplasia and gastritis. He complained about weakness for years, which was relieved in part by over-the-counter dietary supplements. Some years before, after the finding of hypokalaemia (2.6 mmol/L) at a routine examination, he was suggested to take spironolactone that was withdrawn after 1 month because of dizziness.

At the physical examination, the pulse was regular (72 bpm); no heart murmurs, signs of heart failure or arrhythmias were found. Blood pressure was 150/96 mmHg with tendency to orthostatic hypotension.

12-lead ECG was normal. Left ventricular hypertrophy was evident at echocardiography.

Mild atherosclerotic lesions were found at the carotid bifurcation bilaterally, with no stenosis. Hypokalaemia (2.8 mmol/L) was confirmed at the laboratory tests.

After correction of hypokalaemia with KCl supplementation, the patient was screened for PA. Renin was suppressed (direct renin concentration (DRC) <2 mIU/L)); plasma aldosterone concentration (PAC) was high (552 pmol/L), with high aldosterone-to-renin ratio (ARR) 99.65 (ng/dL)/(ng/mL/h) (Table 28.2). Plasma ACTH and cortisol levels were normal.

What elements prompted investigation of PA in our patient?

If present in a patient with arterial hypertension, hypokalaemia, either spontaneous or diuretic-induced, strongly suggests PA. In our patient, chronic symptomatic hypokalaemia was very suggestive for PA.

However, since the first report of normokalaemic PA by Jerome Conn in 1965, it was clear that hypokalaemia should not be considered a prerequisite of PA. As demonstrated in 2006 by the PAPY study, the first large prospective survey that used a rigorous methodology to diagnose PA and aldosterone-producing adenoma (APA), more than 50% of patients with an APA and 82% of those with a bilateral form of PA can present with normal serum levels of potassium. This means that, if only hypokalaemic hypertensive patients are screened for PA, many normokalaemic PA patients would never be screened and diagnosed.

Which patients should be screened for PA?

As stated above, hypokalaemia is one alerting sign of PA, and therefore, hypertensive patients presenting with spontaneous or diuretic-induced hypokalaemia should be screened. Other categories include hypertension (BP >150/100 mmHg) confirmed at repeated measures, drug hypertension resistant to three antihypertensive drugs (including a diuretic), controlled BP (>140/90 mmHg) on four or more antihypertensive drugs, hypertension with incidentally discovered adrenal mass or obstructive sleep apnoea, a family history of early onset of hypertension or stroke at a young age or hypertension with a first-degree relative affected by primary aldosteronism.

However, after the recent prospective PAPPHY (Prospective Appraisal of the Prevalence of Primary aldosteronism in HYpertensive patients presenting with atrial flutter or fibrillation) study showing a high prevalence rate of PA (i.e. 42%) in hypertensive patients presenting with unexplained atrial fibrillation, it has been proposed to include also this category to those indicated by the 2016 Endocrine Society Clinical Practice Guidelines.

Moreover, some experts suggest less restrictive criteria, thereby addressing screening all newly presenting hypertensive patients, particularly those with a high chance of curing hypertension with adrenalectomy, as young subjects with a short duration of hypertension.

Why is it important to screen patients for PA?

Excess aldosterone levels exert deleterious effects on the cardiovascular system and the kidneys.

Patients with PA develop left ventricular hypertrophy, both concentric and eccentric, more frequently than age-, sex- and blood pressure-matched subjects with essential hypertension. PA patients develop cardiac fibrosis with abnormal left ventricular filling and electrophysiological changes that may act as trigger for atrial fibrillation often facilitating its onset during aging.

Moreover, PA accelerates endothelial dysfunction with vascular remodelling of small and large arteries and onset of microalbuminuria. This translates into an increased risk of myocardial infarction, heart failure and arrhythmias, particularly atrial fibrillation and deterioration of the renal function, higher than that developed by matched essential hypertensive patients.

How to screen patients for PA?

The diagnosis of PA is based on demonstration of low or very low levels of renin and inappropriate high levels of aldosterone (PAC, plasma aldosterone concentration). For screening, the aldosterone-to-renin ratio (ARR) is applied (Fig. 28.1). Renin can be determined as direct renin concentration (DRC) and plasma renin activity (PRA). In many centres, DRC has replaced PRA because its determination is cheaper and non-radioactive, allows storage of samples at room temperature, and its measurement can be performed with an automated device.

Use of ARR needs adhesion to some 'rules' addressed to optimize the patient's preparation and determination of ARR (Table 28.1), as discussed below.

How should the patient be prepared for measurements of DRC and PAC?

The careful standardization of the patient, as well as of the assay, is crucial for optimal patient reproducibility.

Hypokalaemia, if present, should be corrected with oral or IV KCl supplementation because it blunts aldosterone secretion and, therefore, could provide a false-negative ARR. Monitoring urinary potassium excretion is a simple and cheap strategy to dose KCl supplements.

Salt intake is crucial for a proper interpretation of the hormonal status. Hence, a 24-h collection of urine is needed to measure urinary sodium excretion, which corresponds to the intake.

Since withdrawal of antihypertensive drugs can be dangerous for the patient, treatment with drugs that have negligible effects on the ARR is recommended. Unfortunately, many antihypertensive drugs interfere with the ARR such as diuretics, angiotensin convertase enzyme inhibitors (ACEI), angiotensin receptor blockers and beta-blockers (Table 28.1). These drugs should be withdrawn 2–6 weeks before taking blood for ARR measurement. Vasodilators as the alpha1-receptor blocker doxazosin and/or the long-acting calcium channel blockers as verapamil or diltiazem are the preferred drugs.

How to interpret ARR?

First of all, the cut-off value of direct renin concentration (DRC) or plasma renin activity (PRA) that provides the best combination of sensitivity and specificity should be identified at each centre. Moreover, since both DRC and PRA lose their precision in the low range, it is needed to set, in each centre, the lowest minimum value to be used for calculation of ARR to avoid overinflation of ARR. Such values are 0.2 ng/mL/h and 2 mIU/L for PRA and DRC, respectively.

ARR should be interpreted considering the salt intake because sodium is one of the most potent factors that affect renin and aldosterone secretion. At our centre, using an automated chemiluminescent assay to measure PAC (ng/dL) and DRC (mIU/L), we found that the optimal ARR cut-off of 2.06 ng/dl/mIU/l (corresponding to 20.6 ng/mIU) provided sensitivity of 92% and specificity of 92% for the identification of APA, with accuracy estimated by the area under the receiver operating characteristic curve of 0.974 (95% CI 0.940 to 0.991). In addition to ARR, basal PAC should be over 15 ng/dL to raise the suspicion for PA. In other centres, using PRA, an ARR over 30 and a basal PAC over 20 ng/dL are usually considered positive.

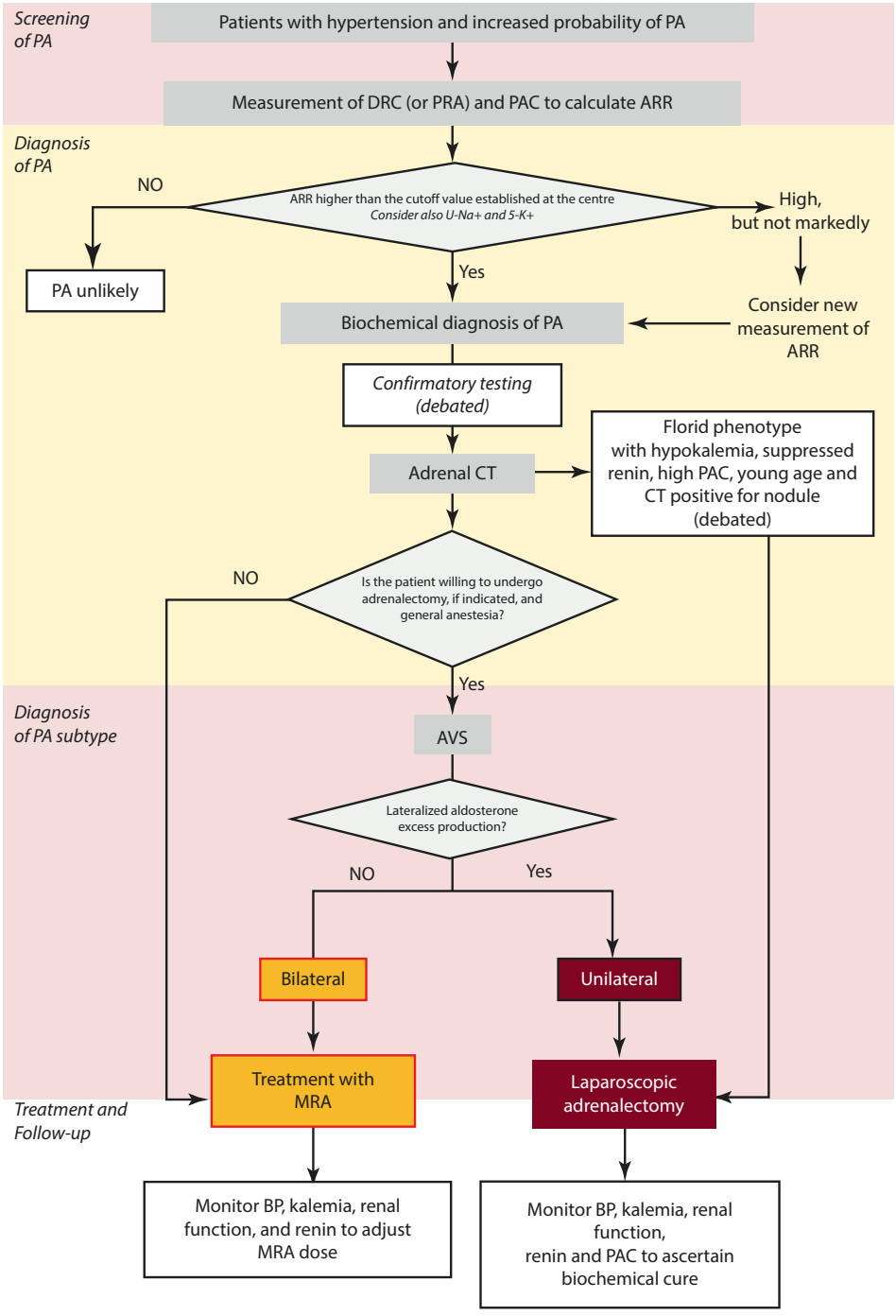

Fig. 28.1 Algorithm for diagnosis of Primary Aldosteronism (PA) and its subtyping. ARR aldosterone-to-renin ratio, AVS adrenal vein sampling, BP blood pressure, CT computed tomography, DRC direct renin concentration, PA primary aldosteronism, PRA plasma renin activity, U-Na+ urinary sodium excretion, S-K+ serum potassium concentration. Debated indicates issues for which no consensus has been reached. (Based on Funder JWW, et al. The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2016; Rossi GP. Primary Aldosteronism: JACC State-of-the-Art Review. J Am Coll Cardiol 2019; and Rossi GP, et al. Disease monitoring of Primary Aldosteronism. Best Practice & Research Clin Endocrinol & Metabolism 2020)

Table 28.1 Blood pressure and laboratory tests at presentation and at 1 month follow-up after surgery

Test	Value	
	At admission	*1-month follow-up*
Blood pressure (mmHg)	170/96	120/80
Basal DRC (mIU/L, normal 2.8–39.0)	<2	4.4
Basal PAC (pmol/L, normal 48–335)	552	135
ARR (ng/dL)/(ng/mL/h)	99.65	14.4
Post captopril challenge DRC (mIU/L)	<2	–
Post captopril challenge PAC (pmol/L)	573	–
Serum potassium levels (mmol/L, normal 3.5–5.0)	3.8[a]	4.5
Urinary sodium excretion (mmol/24 h)	170	155

ARR aldosterone-to-renin ratio, *DRC* direct renin concentration, *PAC* plasma aldosterone concentration

[a]*After correction with oral KCl supplementation*

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Finally, as recently proposed by Rossi (see the suggested review), the ARR should not be interpreted simply as positive or negative, in other words as 'crude bivariate approach' because the same ARR value that can be obtained from different PAC and DRC values could indicate different conditions that require different downstream work-up and treatment.

What tests were then performed in our patient?

The patient, who presented at our centre some years ago, was also investigated with the captopril challenge after the positive ARR screening result, which showed an elevated ARR (Table 28.2). The rationale behind the captopril challenge was that PA is autonomous from angiotensin II; however, this contention has not been proved.

The confirmatory tests, including the oral sodium loading test, the saline infusion test, the captopril challenge test and the fludrocortisone (a synthetic mineralocorticoid) with salt loading test, have been proposed to minimize false-positive results, which are more common if low ARR cut-off values are used for screening. In fact, a low ARR cut-off value enhances sensitivity of the test along increasing the false-positive rates. If those false-positive PA patients are not detected, they could be exposed to invasive tests with no benefit for the patient. Hence, the aim of the so-called confirmatory tests is to exclude the false-positive rates from the downstream work-up of PA, and, therefore, as first proposed by Rossi in Padua, the term confirmatory tests should be replaced by 'exclusion tests'.

The saline infusion test is used in many centres being rather simple. An approach of the test includes 500 mL/hour saline infusion given for 4 hours to the patient. By assuming that PA is autonomous from salt and volume load, the patients with PA will not suppress PAC showing PAC > 10 ng/dL. Oral salt loading and fludrocortisone are also contended to suppress aldosterone secretion in healthy subjects, whereas they fail to do so in patients with autonomous aldosterone production.

A great debate exists on the usefulness of the confirmatory (exclusion) tests. First, at the prevalence rate of PA found at the hypertension centres, their negative predictive value is higher than their positive predictive value, thereby challenging the need for identifying the false-positive PA patients. Moreover, they are based on assumption that hyperaldosteronism is autonomous from the renin-angiotensin system, but such assumption has been never been proven, and moreover, the recent evidences documenting the angio-

Table 28.2 Factors that affect aldosterone-to-renin ratio (ARR) and suggestions for optimizing its interpretation

Factors that affect ARR	Cautions
Serum potassium levels	Correction of hypokalaemia is needed to avoid false-negative ARR values
Salt intake	Low salt intake can increase PAC, providing false-positive ARR values. Salt intake can be easily calculated by measuring 24-hour urinary sodium excretion
Patient position and blood sampling	Preparation of the patient and sampling conditions should be standardized at each centre. Quiet resting supine, or sitting, for 1 hour is recommended because it allows renin and PAC values to return to baseline levels after upright position
Drugs affecting ARR should be withdrawn before testing	Beta-blockers (decrease renin) for at least 2 weeks ACEI and ARB (increase renin) for at least 2 weeks[a] Mineralocorticoid receptor antagonists (spironolactone, canrenone, eplerenone) for at least 4–6 weeks. [b]Other diuretics for at least 2 weeks
Drugs not affecting ARR	Use of α1-receptor blockers (e.g. doxazosin) and long-acting phenylalkylamine-type calcium channel blocker (verapamil) is allowed
Handling and storage of plasma and serum samples	PRA and DRC assays need different modalities of handling and storage
Renin assay	The lowest level of renin to be used for ARR should be fixed at a minimum value (see text for details)
ARR sensitivity and specificity	Each centre should calculate the cut-off value that provides the best combination of sensitivity and specificity

PAC plasma aldosterone concentration
[a]When withdrawal of ACEI is unsafe for the patients, an increase of PAC under ACEI is suggestive of PA
[b]A recent evidence from the controlled EMIRA study showed that canrenone did not affect ARR, suggesting that this issue is still open

tensin receptors in the human adrenocortical tissue are against this contention. Further support came from the large AQUARR study that, investigating a retrospective and a prospective validation cohort, demonstrated that the captopril challenging test did not provide any diagnostic gain over the basal ARR when carefully performed and interpreted.

Following the 2016 Endocrine Society Clinical Practice Guidelines, no need for the exclusion tests can be envisaged in patients with a florid PA phenotype. A simplified diagnostic algorithm that does not include the exclusion tests has been recently suggested, as in the case of a patient presenting with markedly high ARR, for whom the AVS can be proposed directly with no further laboratory test.

What further tests should be performed in PA patients?

In our patient, further investigation included CT of the abdomen, which showed a node (10 x 8 mm) in the right adrenal gland. The left adrenal vein drained into the ipsilateral renal vein, whereas the right adrenal vein in the inferior vena cava.

Then, after having ascertained the patient's will of searching surgical cure with adrenalectomy, adrenal venous sampling (AVS) was performed. Hyper-incretion of aldo-

sterone from the right adrenal gland was found, and the patient underwent right adrenalectomy, with no complications.

At pathology, an adenoma consisting of glomerular (90%) and fasciculata (10%) cells was detected, with some micronodules in the cortical zone.

At post-surgery day 1, both blood pressure and serum potassium levels returned to normal and remained normal at 1- and 6-month follow-up. DRC and PAC normalized at 1-month follow-up.

What is the role of imaging in the work-up of PA?

Imaging with CT or MR is useful to detect adrenal masses that, when large, are suggestive for carcinoma. Moreover, imaging provides information on the anatomy of adrenal veins and their drainage, which are relevant for the interventional radiologist who will perform AVS.

However, CT and MR imaging cannot prove function of the adrenal masses and, therefore, cannot localize the source of aldosterone excess. Furthermore, aldosterone-producing microadenomas cannot be detected, because of their tiny size by CT or MR imaging, and in most cases of idiopathic hyperaldosteronism, no apparent change in the morphology of the adrenal glands is evident.

A well-known study from the Mayo Clinic found that the diagnostic accuracy of CT imaging for discriminating unilateral from bilateral forms of PA was very poor, with concordance to the AVS results in only about 50% of the cases. Of note, about 20% of unilateral PA at AVS were missed with CT. This means that if subtyping of PA is based on CT (not on AVS), 20% of unilateral forms of PA would not receive any chance of cure PA with adrenalectomy. Moreover, not less important, in more than 20% of cases, bilateral forms were misdiagnosed as unilateral, meaning that, if AVS is not performed, unnecessary adrenalectomy would be performed. Hence, AVS is essential to distinguish between unilateral and bilateral PA.

What is the role of AVS in the work-up of PA?

AVS is the gold standard test to discriminate between unilateral and bilateral forms of PA (Fig. 28.1). Discrimination is fundamental because the treatment is surgical in the first case and medical in the latter.

How is AVS performed?

The procedure consists of the collection of blood samples from the inferior vena cava and the adrenal veins (bilaterally in simultaneous or sequential collection) to measure cortisol and aldosterone (cortisol is needed to confirm the appropriate position of the catheter). Careful preparation of the patient for the procedure mostly includes correction of hypokalaemia and withdrawal of interfering drugs.

AVS should be performed by a well-trained radiologist to minimize the risks of complications, mostly the rupture of the adrenal vein. However, if performed by an expert interventionist, such risk is negligible.

Interpretation of AVS results requires skill and experience. Moreover, no consensus exists on the standards to be used for the AVS procedure and the criteria for data interpretation.

The most used indices to interpret AVS data are the selectivity index, which is a measure of the adequacy of the cannulation, and the lateralization index, which allows the detection, if present, of lateralization of the excess aldosterone production. The selectivity index is calculated as the ratio between the cortisol plasma levels (C) in the right or left adrenal vein and the

inferior vena cava. In most centres, the cut-off is set up to 2. In the presence of bilaterally selective AVS, the lateralization of aldosterone (A) secretion can be assessed when the ratio of aldosterone to cortisol on the side with the higher ratio (A/C side) over the contralateral aldosterone to cortisol (A/C contralateral) is greater than 2 (or 4, or 5 depending on the cut-off established at each centre for basal and/or dynamic AVS). In some centres, a dynamic adrenal vein sampling with ACTH (adrenocorticotropic hormone) is used to minimize bias caused by the circadian rhythm of aldosterone. Usefulness of dynamic AVS is also a debated issue, for which no consensus has been reached yet.

Due to its complexity, AVS is not used at all centres. Lack of AVS could lead to adrenalectomy without unequivocal demonstration of lateralized excess aldosterone production, with the risk of removing the non-culprit adrenal gland, or missed diagnosis of unilateral form of PA, with no chance of curing PA with adrenalectomy. Moreover, recent studies show that co-secretion of aldosterone and cortisol from adrenal tumours might make the interpretation of the results more difficult.

Who should not undergo AVS?

The following categories of PA patients with:

(a) Contraindications to general anaesthesia and/or surgery
(b) Willingness of medical treatment
(c) Familial hyperaldosteronism caused by germline mutations
(d) Suspicion of adrenocortical carcinoma because of the large size of the adrenal tumour

Following the guidelines, AVS could be also omitted in young patients (<35 years) with a florid PA phenotype (e.g. with spontaneous hypokalaemia), undetectable renin, high PAC and unilateral cortical adenoma with contralateral normal adrenal at imaging. This suggestion is based on reports documenting rarity of non-functioning adrenocortical adenomas (the so-called incidentaloma (▶ Chap. 26)) in young people. However, some experts recommend caution in addressing such patients directly to surgery because of the paucity of evidences on this matter.

What is the treatment for PA?

Surgery, i.e. adrenalectomy, is the treatment for APA, whereas the bilateral forms should be treated pharmacologically. Mineralocorticoid receptor antagonists, such as spironolactone, potassium canrenoate and the more selective eplerenone, are the recommended drugs that contrast hypokalaemia and the adverse effect of aldosterone. The necessary dose of spironolactone is usually low (25–50 mg/day). Eplerenone can be better tolerated in males, as it lacks anti-androgenic activity, but it is less effective.

Is follow-up needed for PA patients?

Yes, follow-up is crucially important.

Diagnosis of APA, which is the only PA form that can be diagnosed unequivocally, can be defined conclusively at follow-up after adrenalectomy, based on demonstration of biochemical cure, pathology and immunohistochemistry. Hence, diagnosis of APA can be based on the 'five-corner criteria', which include:

1. Biochemical diagnosis of PA
2. Unequivocal evidence of lateralized aldosterone secretion at AVS
3. Evidence of a nodule at pathology
4. Correction of the biochemical picture of PA after adrenalectomy
5. Detection of a CYP11B2 (aldosterone synthase)-positive adenoma in the resected adrenal cortex at immunohistochemistry with a monoclonal antibody for human CYP11B2

Can PA be inherited?

There are rare familial forms of PA whose genetic background has been clarified. The most frequent is the type 1 familial aldosteronism (glucocorticoid remediable aldosteronism), caused by a fusion gene consisting of the gene regulating promoter sequence from cortisol synthase (CYP11B1) and the coding region of aldosterone synthase (CYP11B2). The fusion gene is expressed in the zona fasciculata and is under ACTH regulation. The treatment of this condition is quite different from the sporadic forms, as ACTH suppression by a synthetic glucocorticoid lacking mineralocorticoid activity, i.e. dexamethasone is the mainstay of treatment.

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Tips

The reader is advised to read the next chapter on secondary aldosteronism (► Chap. 29). For the differential diagnosis of hypertension and hypokalaemia, the chapters on 17α-hydroxylase/17,20 lyase deficiency (► Chap. 35) and ectopic ACTH syndrome (► Chap. 45) are worth reading.

Take-Home Messages

- Primary aldosteronism (PA) is the most common form of endocrine hypertension.
- Case detection testing for PA should be performed by measuring the aldosterone-to-renin ratio.
- Screening for PA is important because the excess aldosterone levels exert deleterious effects on the cardiovascular system and the kidneys.
- Adrenal venous sampling is the gold standard test to discriminate between unilateral and bilateral forms of PA. Discrimination is fundamental because the treatment is surgical in the first case and medical in the latter.
- The follow-up is recommended in both adrenalectomized and medically treated PA patients.

Acknowledgements The author would like to express her gratitude to Prof. Gian Paolo Rossi for critically discussing the cases of primary aldosteronism that presented to the Hypertension Unit of the University of Padova and for opening novel unexplored horizons to the research team.

Suggested Reading

1. Funder JWW, Carey RMM, Mantero F, Murad MHH, Reincke M, Shibata H. The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101:1889–916. https://doi.org/10.1210/jc.2015-4061.
2. Monticone S, Burrello J, Tizzani D, Bertello C, Viola A, Buffolo F, Gabetti L, Mengozzi G, Williams TA, Rabbia F, Veglio F, Mulatero P. Prevalence and clinical manifestations of primary aldosteronism encountered in primary care practice. J Am Coll Cardiol. 2017;69:1811–20. https://doi.org/10.1016/j.jacc.2017.01.052.
3. Rossi GP, Bernini G, Caliumi C, Desideri G, Fabris B, Ferri C, Ganzaroli C, Giacchetti G, Letizia C, Maccario M, Mallamaci F, Mannelli M, Mattarello M-J, Moretti A, Palumbo G, Parenti G, Porteri E, Semplicini A, Rizzoni D, Rossi E, Boscaro M, Pessina AC, Mantero F, PAPY Study Investigators. A prospective study of the prevalence of primary aldosteronism in 1125 hypertensive patients. J Am Coll Cardiol. 2006;48:2293–300. https://doi.org/10.1016/j.jacc.2006.07.059.
4. Rossi GP. Primary aldosteronism: JACC State-of-the-Art review. J Am Coll Cardiol. 2019;74:2799–811. https://doi.org/10.1016/j.jacc.2019.09.057. *The reader is referred to this updated review for full bibliography.*
5. Rossi GP. Update in adrenal venous sampling for primary aldosteronism. Curr Opin Endocrinol Diabetes Obes. 2018;25:160–71. https://doi.org/10.1097/MED.0000000000000407.
6. Rossitto G, Cesari M, Ceolotto G, Maiolino G, Seccia TM, Rossi GP. Effects of mineralocorticoid and AT-1 receptor antagonism on the aldosterone – renin ratio (ARR) in primary aldosteronism patients

(EMIRA Study): rationale and design. J Hum Hypertens. 2018;33:167–71. https://doi.org/10.1038/s41371-018-0139-x.

7. Seccia TM, Caroccia B, Gomez-Sanchez EP, Vanderriele PE, Gomez-Sanchez CE, Rossi GP. Review of markers of zona glomerulosa and aldosterone-producing adenoma cells. Hypertension. 2017;70:867–74. https://doi.org/10.1161/HYPERTENSIONAHA.117.09991.

8. Vaidya A, Mulatero P, Baudrand R, Adler GK. The expanding spectrum of primary aldosteronism: implications for diagnosis, pathogenesis, and treatment. Endocrine Rev. 2018;39:1057–88. https://doi.org/10.1210/er.2018-00139.

Secondary Aldosteronism

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Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_29

Opening

The renin-angiotensin-aldosterone system (RAAS) takes a major role in the regulation of blood pressure. The main effector molecules are angiotensin II and aldosterone via mechanisms including constriction of peripheral resistance vessels and glomerular arterioles, renal reabsorption of sodium and water, and increase in the sympathetic outflow and generation of dipsogenic signals within the central nervous system. This process turns also into increasing renal loss of potassium and hydrogen ion, leading to hypokalemia and metabolic alkalosis.

This chapter deals with conditions leading to aldosterone overproduction (except for primary aldosteronism discussed in ► Chap. 28) and in most cases to hypertension as a consequence.

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Definition of the Disease

The juxtaglomerular apparatus is responsible for the regulation of renin release. Renin secretion as the rate-limiting step for angiotensin II production is evoked mainly by decreasing renal blood flow and beta-adrenergic sympathetic signals.

Aldosterone secretion is principally triggered by angiotensin II, but adrenocorticotropic hormone (ACTH) also potentiates it, whereas hypokalemia has an inhibitory effect on it.

The overstimulation of this classical neurohumoral cascade of RAAS is called secondary aldosteronism. Please note that this is first of all a physiological regulatory process, which might appear also inappropriately in various pathological or pharmacological settings. Beta-adrenergic receptor blockers and central alpha-adrenergic agonists lower plasma renin activity, while diuretics (including mineralocorticoid receptor antagonists), angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs) increase plasma renin activity. These medications should be withdrawn or substituted before the hormonal investigations (at least for 4–6 weeks with mineralocorticoid receptor antagonists and potassium-sparing diuretics and 2 weeks in general for other drugs). Preferred antihypertensive drugs during investigations including renin and aldosterone measurements are non-dihydropyridine (phenylalkylamine type) calcium channel blockers and alpha-adrenergic receptor blockers. (These issues are discussed in the preceding chapter on primary aldosteronism as well (► Chap. 28).)

The plasma renin activity and aldosterone concentration are optimally measured from samples taken in the morning. Unrestricted dietary salt intake is important prior to testing, as well as normokalemia. The positive or negative effect on plasma renin activity of a certain drug must be taken into consideration during the interpretation of hormonal results.

Case Presentation

A 21-year-old female patient was referred to our tertiary referral endocrine center with resistant hypertension diagnosed at the age of 18 years. Her blood pressure was high (maximum 190–200/100–110 mmHg) despite a triple combination of antihypertensive drugs (ACEI, calcium channel blockers, and diuretics).

On her first visit, we measured equally elevated blood pressure on both arms (180/100 mmHg) and significantly lower blood pressure on both lower extremities (150/80 mmHg).

Routine laboratory examinations revealed normal serum creatinine, blood urea nitrogen, potassium, and sodium levels, with no signs of hyperlipidemia or diabetes mellitus. Chest X-ray showed no abnormalities. Echocardiography revealed normal ventricular function. Native abdominal and pelvic CT scan showed no abnormality in the renal and adrenal regions.

Hormonal investigations were performed after the withdrawal of antihypertensive drugs affecting the RAAS. The laboratory results confirmed hyperreninemic hyperaldosteronism: supine aldosterone concentration was 17.2 ng/dL (reference range 0.7–15.0 ng/dL), and plasma renin activity was 4.41 ng/mL/hour (reference range 0.20–2.80 ng/mL/hour). The patient was euthyroid and eucortisolemic, and urinary metanephrines were within the normal range (Table 29.1).

Diagnostic imaging workup was performed to investigate the cause of secondary aldosteronism. Both kidneys showed normal morphology by ultrasonography, and their parenchymal function and drainage were also normal by functional ^{99m}Tc-renal scintigraphy.

Abdominal CT angiography (Fig. 29.1) revealed a narrowed segment (8 mm luminal diameter) of the aorta at the diaphragmatic level. The extension of this investigation to the thoracic region (Fig. 29.1) confirmed a funnel-like stenosis of the descending aorta with a minimum diameter of 6 mm at the level of the X–XI thoracic vertebrae. This was followed by a post-stenotic dilatation of 14 mm and another distal narrowing seen already on the abdominal scan.

Percutaneous transluminal stent graft implantation followed by balloon catheter dilatation was performed (Fig. 29.2) with success, as her blood pressure normalized after the intervention.

However long-term blood pressure control was still required.

Table 29.1 Hormonal examinations

Hormone	Measured values	Normal range
Morning serum cortisol	232.6 nmol/L	220–690 nmol/L
Late night serum cortisol	45.2 nmol/L	<138 nmol/L
Morning salivary cortisol	0.326 μg/dL	<0.690 μg/dL
Late night salivary cortisol	0.054 μg/dL	<0.430 μg/dL
Urinary cortisol	147.7 nmol/die	100.0–379.0 nmol/die
Adrenocorticotropic hormone	12.0 pg/mL	7.2–63.3 pg/mL
Dehydro-epi-androsterone sulfate	118.3 μg/dL	130.0–430.0 μg/dL
Aldosterone supine	**17.2 ng/dL**	0.7–15.0 ng/dL
Renin activity supine	**4.41 ng/mL/hour**	0.20–2.80 ng/mL/hour
Urinary adrenaline	2.9 μg/die	4–20 μg/die
Urinary noradrenaline	46 μg/die	23–105 μg/die
Urinary dopamine	483.6 μg/die	62–446 μg/die
Urinary metanephrine	59.3 μg/die	<275 μg/die
Urinary normetanephrine	152.1 μg/die	<550 μg/die
3-methoxytyramine	106.7 μg/die	<460 μg/die
Thyroid-stimulating hormone	0.474 mIU/L	0.35–4.95 mIU/L

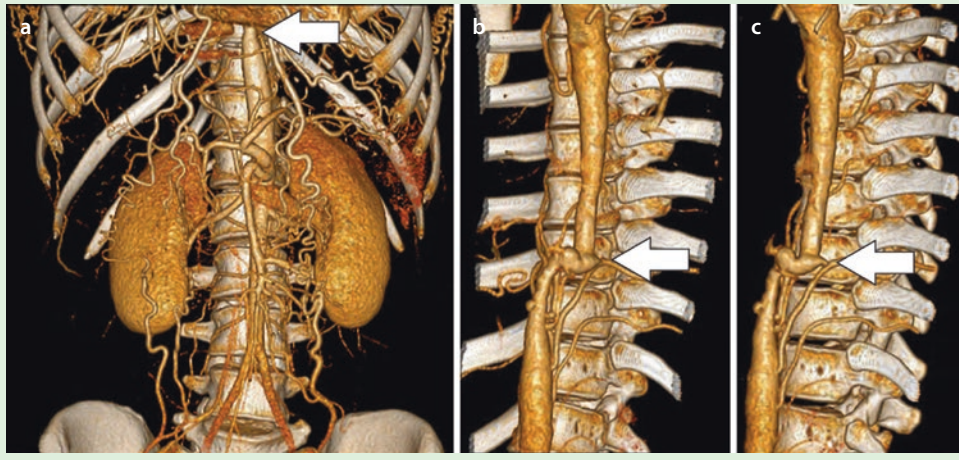

Fig. 29.1 Three-dimensional reconstruction of computed tomography angiography: **a** Abdomen (anterior view); **b** thoracic aorta (anterior view); **c** thoracic aorta (lateral view). Arrow: the stenotic segment of the aorta

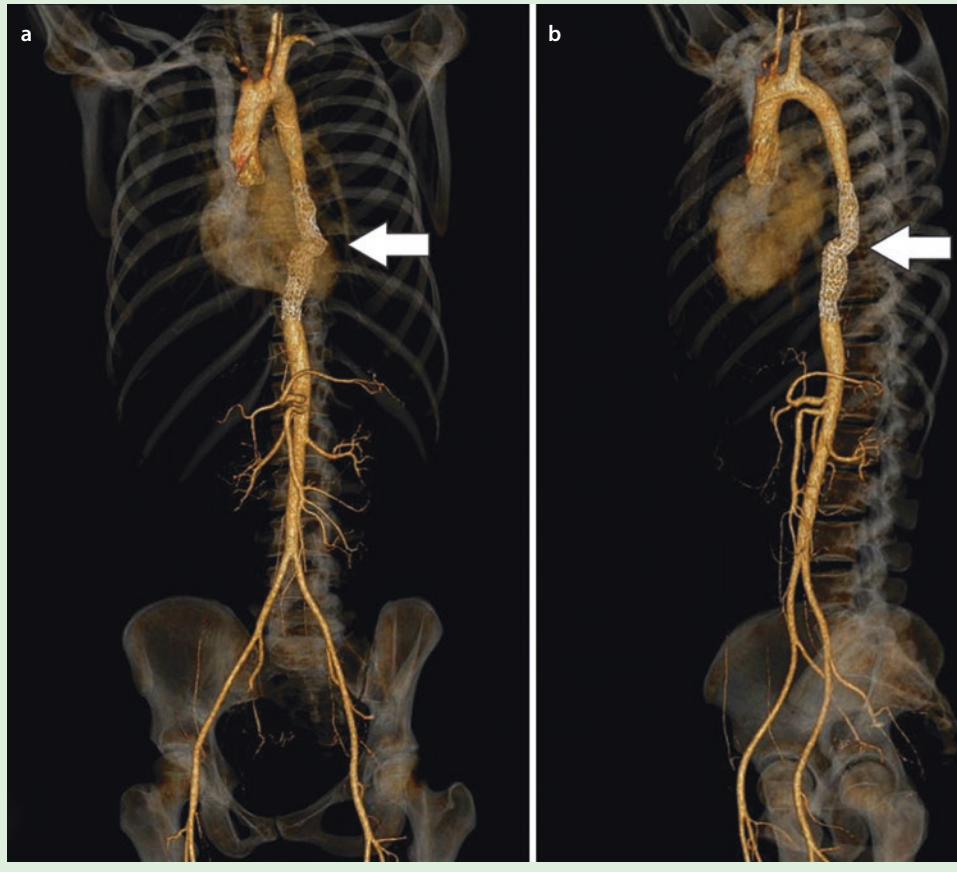

Fig. 29.2 Three-dimensional reconstruction of computed tomography angiography after intervention: **a** Anterior view; **b** lateral view. Arrow: stent-graft in the thoracic aorta

When to suspect secondary hypertension?

Most hypertensive patients are classified as having essential (primary) hypertension, whereas secondary hypertension is present in 5–10% of all cases. In contrast to essential hypertension that can only be treated, secondary hypertension can often be healed.

In hypertensive patients, the following cases are suggestive of secondary hypertension (variations in definitions and cut-off values exist in the literature):

- Severe (grade 3) hypertension or hypertension with coexistent evidence of acute end-organ damage (malignant hypertension)
- Resistant hypertension defined as inadequate control of blood pressure despite the use of three or more different antihypertensive agents in combination (including a diuretic), with adequate dosing
- Sudden and persistent worsening of a previously well-controlled hypertension (accelerated hypertension)
- First presentation in young age (less than 30 years or less than 40 years with at least grade 2 hypertension)
- First presentation after the age of 55 years
- Clinical or biochemical characteristics of certain endocrine or renal diseases (see below and Tips) including, e.g. hypokalemia and metabolic alkalosis
- Familial aggregation of early-onset hypertension or disorders causing secondary hypertension
- Hypertension and sleep apnea

What kind of endocrine diseases can lead to secondary hypertension?

The most common endocrine cause of secondary hypertension is primary aldosteronism (▶ Chap. 28). Among other adrenal diseases leading to hypertension, pheochromocytoma (▶ Chap. 37) and rare forms of congenital adrenal hyperplasia (11β-hydroxylase and 17α hydroxylase/17,20-lyase deficiency (▶ Chap. 35)) should be highlighted. Hypertension is common in all forms of hypercortisolism (pituitary Cushing's disease (▶ Chap. 3), adrenal Cushing's syndrome (▶ Chap. 27), and ectopic ACTH syndrome (▶ Chap. 45)). Hypothyroidism (▶ Chap. 11) can be associated with hypertension due to increased peripheral resistance, but hypotension might also occur, and most patients with hypothyroidism are normotensive. Hyperthyroidism (▶ Chap. 12) can lead to systolic hypertension due to hyperkinetic circulation. Acromegaly (▶ Chap. 2) can also be associated with hypertension. Secondary aldosteronism is discussed in detail here in this chapter.

What raised awareness for the possibility of an aortic pathology in this case?

First of all, physical examination should be extended to the blood pressure measurement of both arms (as always at the first consultation of a new patient) and in all possible cases of secondary hypertension to the lower extremities as well. The aortic coarctation predominantly occurs as a diaphragm-like ridge pushing into the aortic lumen at the level immediately distal to the left subclavian artery causing elevated blood pressure in the arms compared to the legs. In some cases, the narrowing is immediately proximal to the left subclavian artery causing lower values also in the left arm.

Beside the differences in blood pressure values, the classic triad of aortic coarctation consists of delayed and sometimes hardly palpable femoral pulses compared to the ones over the radial artery and vascular bruits along the course of the aorta or the pronounced collateral branches (internal thoracic, subclavian, or intercostal arteries).

The mid-aortic syndrome is a rare form of the aortic coarctation involving the abdominal aorta and/or distal descending thoracic aorta and can include the renal and visceral branches as well. The major-

ity of the cases are idiopathic, while others are caused by acquired inflammatory diseases such as Takayasu arteritis and intrauterine rubeola infection or are associated with Mendelian disorders such as neurofibromatosis type 1 and Williams syndrome (a complex developmental abnormality caused by hemizygous deletion of 1.5–1.8 Mb on chromosome 7q11.23).

Hormonal investigations showing secondary aldosteronism corroborated the suspicion for aortic coarctation.

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What is the pathomechanism of secondary hypertension in aortic coarctation?

Three main theories have evolved about the components of hypertension in aortic coarctation. The first is the mechanical obstruction to the blood flow causing the elevation of blood pressure in the upper extremities. There is another possible mechanism, the so-called neural theory of baroreceptor resetting, resulting in blood pressure elevation in order to maintain circulation in the lower body parts. The third possible mechanism is the consequence of renal hypoperfusion leading to enhanced renin and aldosterone secretion and subsequent volume expansion.

How to discriminate between primary and secondary aldosteronism?

Here we refer also to the preceding chapter on primary aldosteronism (▶ Chap. 28), where elevated plasma aldosterone concentration coexists with suppressed plasma renin.

Contrary to primary aldosteronism, secondary aldosteronism is associated with an elevated plasma aldosterone usually accompanied by an elevated but certainly not suppressed plasma renin activity.

It is, however, to be noted that normal values of plasma renin activity and plasma aldosterone concentration do not exclude secondary aldosteronism (see below).

What are the features of renovascular stenosis/hypertension?

While one kidney is usually enough for the "detoxification" function, the hypoperfusion of one kidney or even a part of it can be a signal strong enough to trigger secondary aldosteronism.

Atherosclerosis of the renal artery is the most common cause of renovascular hypertension, while fibromuscular dysplasia is far less frequent and affects mostly younger patients with a female predominance. Other causes like aneurysms, tumors, and retroperitoneal fibrosis are even less frequent.

The gold standard method is renal arteriography to confirm the stenosis (50–70%, depending on the source), but Doppler ultrasonography (with an expert examiner!), CT or MR angiography, and renal scintigraphy are noninvasive alternatives. Since only a proportion of patients with renal vascular disease have renovascular hypertension, thus structural abnormalities must be strengthened with functional studies.

In renal artery stenosis, the best medical therapy is essential with special emphasis on ACEIs or ARBs for blood pressure control of unilateral cases, whereas revascularization (surgery and transarterial stenting or balloon angioplasty) is recommended only for special patient groups (mostly in fibromuscular dysplasia). It is very important to note that ACEIs or ARBs are contraindicated in bilateral renovascular stenosis as they can precipitate acute renal insufficiency.

What kind of other renin-mediated secondary hypertension forms related to renal involvement should be mentioned?

The intrarenal vascular baroreceptor mechanism is triggered by focal intrarenal pathologies as well, like an infarction within the kidney or vasculitis with renal involvement. From the latter group, poly-

arteritis nodosa causes most frequently renin-mediated hypertension. This is a rare disease affecting small-diameter vessels. General symptoms are fever, arthralgia, and weight loss. In the kidney, saccular microaneurysms cause tissue compression with incomplete focal circulatory dysfunctions, which might be accompanied by proteinuria, hematuria, azotemia, or even aneurysmal bleeding. The diagnosis rests on angiography and histology.

- Polycystic kidney disease can also lead to secondary aldosteronism via tissue compression and the intrarenal vascular baroreceptor mechanism. Two monogenic forms are known (mutation of *PKD1* and *PKD2* genes). If there is suspicion for the disease (familial disease, bilateral cysts, coexistent pancreatic or liver cysts, circle of Willis aneurysm), the use of CT or MRI is mandatory since in early stages, ultrasonography is not sensitive enough and kidney function is still normal. Cyst decompression can lower blood pressure at least temporarily.

Do normal plasma aldosterone concentration and plasma renin activity rule out hypertension due to renal hypoperfusion?

- Interesting data were obtained from studies on patients with aortic coarctation or renovascular hypertension suggesting that extracellular volume expansion can mask secondary aldosteronism resulting in normal plasma aldosterone concentration and plasma renin activity since the consequent elevation of blood pressure is able to restore the renal perfusion.

- In the past, several methods were used to unmask this phenomenon and enable the identification of the hyperreninemic hyperaldosteronism, such as dietary salt restriction, diuretic treatment, or the so-called captopril test (► Chap. 28). All these signals provoke per se an increase in plasma renin activity but with a greater magnitude in renal hypoperfusion compared to an intact renal circulation.

- To the best of our knowledge, this practice is not incorporated to any current diagnostic guidelines, most probably because of the advent and wide availability of the high-precision imaging tools for the assessment of aortic or renovascular pathology. However, in cases when there is a high suspicion for renal hypoperfusion, and the required imaging methods are unavailable, or their results are contradictory, this possibility might be kept in mind during the interpretation of the hormonal results.

How to rule out renal hypoperfusion then if the hormonal findings are normal?

- Regarding aortic coarctation, the differences in blood pressure and pulse characteristics between the upper and lower parts of the body necessitate extensive imaging (echocardiography and abdominal Doppler ultrasound, CT or MR angiography, aortography). On the contrary, the absence of these findings is usually enough to rule out aortic coarctation; however the existence of a strong collateral system can mask these physical alterations.

- The case of renovascular hypertension requires a more complex approach. Its clinical suspicion is equal to that of secondary hypertension, and it is strengthened when any of the following phenomena are found without an alternative explanation: abdominal bruits, difference in renal size or bilateral renal atrophy, acute or chronic kidney disease, onset before the age of 30 years or after 55 years, deterioration in kidney function or "flash" (suddenly developing) pulmonary edema after initiation of ACEI or ARB treatment, biochemical evidence of secondary aldosteronism with or without hypokalemia and metabolic alkalosis. However, the absence of these phenomena is not sufficient to rule out renovascular hypertension. The complexity of this disease is marked also by the fact that a stenosis found incidentally on a renal artery is not sure to represent the cause of the hypertension of that patient

since essential hypertension may present also in this clinical setting.

The above-mentioned imaging methods are to be used for the confirmation or exclusion of renal artery stenosis, but guidelines are not consistent in the indication and depth of these investigations in certain patient groups. Each case has to be dealt with on an individual basis.

Is there a possibility of an autonomous renin secreting tumor as an analogy of primary aldosteronism and other hormone producing tumors?

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Yes, but juxtaglomerular cell tumor, also called reninoma, is an extremely rare entity. About 100 cases have been described, most of them were benign and occurred in younger adults. Severe hypertension with markedly elevated plasma renin activity and aldosterone concentration and hypokalemia are characteristic features. The mass lesion in the kidney is frequently tiny, and kidney vein catheter sampling can be very helpful in the diagnosis. The removal of the tumor is curative in most cases. Even less frequently other tumors were described to secrete renin, e.g. adrenocortical carcinoma, hepatoblastoma, Wilms' tumor, and uterus leiomyosarcoma.

Which forms of secondary aldosteronism are not associated with hypertension?

Rare conditions causing secondary aldosteronism without hypertension are represented by the group of sodium losing renal tubulopathies, a heterogeneous group with inherited dysfunctions of one or more renal transepithelial ion channels. Among others, the autosomal recessive Bartter and Gitelman syndrome should be mentioned. Due to the ion channel dysfunction, high concentration of NaCl reaches the macula densa resulting in renin hypersecretion and secondary aldosteronism. (Note that diuretics have a similar way of action.)

The clinical signs of Bartter syndrome (loss-of-function mutations of the bumetanide-sensitive Na-K-2Cl cotransporter) emerge in childhood or even in fetal period and include polyuria and hyposthenuria (possibly with polyhydramnion and premature birth), hypovolemia, renal salt wasting, osteopenia and nephrocalcinosis due to hypercalciuria, hypokalemic alkalosis, and hypocalcemia (even tetany and seizures are possible depending on the severity of the disease). Gitelman syndrome, on the other hand, is mostly diagnosed in adulthood due to severe hypokalemia and hypomagnesemia that is caused by loss-of-function mutations of the thiazide-sensitive Na-Cl transporter. As with Bartter syndrome, secondary aldosteronism with high renin and aldosterone is observed, but low magnesium and decreased urinary calcium excretion are seen.

It should be mentioned here that Liddle syndrome, another "channelopathy" caused by mutations of the epithelial sodium channel inherited as an autosomal dominant trait, leads to severe hypertension and hypokalemia, but both renin and aldosterone are low (it is therefore not a form of secondary aldosteronism).

It is also worth mentioning that most of the chronic kidney diseases are accompanied by various degrees of secondary aldosteronism. The decline in the number of functioning nephrons puts work overload to other nephrons, which develop glomerulosclerosis while hyperfunctioning, and the parallel decrease in hydrostatic pressure leads to secondary aldosteronism.

Secondary aldosteronism is also a well-known phenomenon in other chronic conditions with decreased effective circulating blood volume or cardiac output such as congestive heart failure, liver cirrhosis, nephrotic syndrome, and chronic diuretic use. In these cases, secondary aldosteronism mostly just contributes to the maintenance of normotension. Secondary

aldosteronism is also part of the complex neurohumoral changes occurring during pregnancy which are beyond the scope of this chapter.

Tips

The reader is advised to read the preceding chapter on primary aldosteronism (▶ Chap. 28) before reading this chapter. Moreover, the chapters presenting diseases with secondary hypertension including hypercortisolism (pituitary Cushing's disease (▶ Chap. 3), adrenal Cushing's syndrome (▶ Chap. 27)), pheochromocytoma (▶ Chap. 37), and 17α-hydroxylase/17,20-lyase deficiency (▶ Chap. 35) would also be interesting to the reader.

Take-Home Messages

- Secondary aldosteronism is characterized by high aldosterone and high or non-suppressed renin levels.
- It is important to withdraw as many interacting drugs as possible for a minimum of 2–4 weeks (depending on the drug) and to provide ad libitum access to salt for the patient and ensure normokalemia.
- Normal plasma aldosterone concentration and plasma renin activity do not rule out secondary aldosteronism.
- Vascular stenosis (mostly renovascular) is a major cause of secondary aldosteronism, but there are forms of secondary aldosteronism without hypertension as well (e.g., renal tubulopathies, chronic diseases such as heart failure, liver cirrhosis, nephrotic syndrome, and chronic use of diuretics).
- If renovascular hypertension is suspected and vascular repair is a possible treatment option, an individualized treatment strategy is warranted.
- Measure blood pressure at least once on the lower extremities as well for patients with possible secondary hypertension.

Acknowledgments The authors would like to express their acknowledgment to Professor Péter Sótonyi (Heart and Vascular Center, Semmelweis University, Budapest, Hungary) for the vascular intervention and to Dr. Gergely Kiss (Department of Transplantation and Surgery, Semmelweis University, Budapest, Hungary) for the three-dimensional reconstruction of CT angiography images.

Suggested Reading

1. Brickner ME, Hillis LD, Lange RA. Congenital heart disease in adults. First of two parts. N Engl J Med. 2000;342:256–63. https://doi.org/10.1056/nejm200001273420407.
2. Corry DB, Tuck ML. Secondary aldosteronism. Endocrinol Metab Clin North Am. 1995;24:511–29. https://doi.org/10.1016/S0889-8529(18)30029-X.
3. Inam R, Gandhi J, Joshi G, Smith NL, Khan SA. Juxtaglomerular cell tumor: Reviewing a cryptic cause of surgically correctable hypertension. Curr Urol. 2019;13:7–12. https://doi.org/10.1159/000499301.
4. Kurtz A. Control of renin synthesis and secretion. Am J Hypertens. 2012;25:839–47. https://doi.org/10.1038/ajh.2011.246.
5. Parker FB Jr, Farrell B, Streeten DH, Blackman MS, Sondheimer HM, Anderson GH Jr. Hypertensive mechanisms in coarctation of the aorta. Further studies of the renin-angiotensin system. J Thorac Cardiovasc Surg. 1980;80:568–73. https://doi.org/10.1016/S0022-5223(19)37743-8.
6. Safian RD, Textor SC. Renal-artery stenosis. N Engl J Med. 2001;344:431–42. https://doi.org/10.1056/nejm200102083440607.
7. Saint-Lézer A, Kostrzewa E, Viallard JF, Grenier N, Doutre MS. Secondary hyperaldosteronism in a patient with polyarteritis nodosa and renal artery aneurysms. Joint Bone Spine. 2011;78:524–6. https://doi.org/10.1016/j.jbspin.2011.03.012.
8. Seyberth HW, Weber S, Kömhoff M. Bartter's and Gitelman's syndrome. Curr Opin Pediatr. 2017;29:179–86. https://doi.org/10.1097/mop.0000000000000447.
9. Te Riet L, van Esch JH, Roks AJ, van den Meiracker AH, Danser AH. Hypertension: renin-angiotensin-aldosterone system alterations. Circ Res. 2015;116:960–75. https://doi.org/10.1161/circresaha.116.303587.
10. Torres VE, Donovan KA, Scicli G, Holley KE, Thibodeau SN, Carretero OA, Inagami T, McAteer JA, Johnson CM. Synthesis of renin by tubulocystic epithelium in autosomal-dominant polycystic kidney disease. Kidney Int. 1992;42:364–73. https://doi.org/10.1038/ki.1992.297.
11. White RH, Schambelan M. Hypertension, hyperreninemia, and secondary hyperaldosteronism in systemic necrotizing vasculitis. Ann Intern Med. 1980;92:199–201. https://doi.org/10.7326/0003-4819-92-2-199.

Adrenocortical Cancer

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Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_30

Opening

In this chapter, the reader will learn about the clinical presentation, diagnosis, and management of adrenocortical cancer (ACC), a rare and aggressive endocrine tumor springing from the adrenal cortex. Given that ACC has a grim prognosis, a prompt recognition and adequate management of the tumor and the associated endocrine syndromes is mandatory to improve the chance of survival of affected patients.

Definition of the Disease

ACC is a rare cancer of the endocrine system with an annual incidence of 0.5–2 cases per million population. However, ACC is included in the differential diagnosis of an adrenal incidentaloma that is a quite frequent condition. As many diseases of the adrenal gland, ACC is affecting more frequently women that account for 55–60% of the overall patient series. ACC has a devastating impact on the life of patients and their relatives, since it shortens considerably life expectancy and impairs remarkably quality of life with health-related issues due to cancer progression, hormonal excess, and treatment-related toxicity. This grim picture is even worsened by the fact that ACC is frequent in young subjects, and women are frequently affected in childbearing age.

Since treatment has limited efficacy when the disease is advanced, securing a prompt diagnosis of ACC is key to obtain a complete surgical removal of the tumor, thus avoiding, or delaying, disease progression. Conversely, diagnosis of ACC is often overlooked with other more frequent conditions, thus delaying a specific treatment. Radical resection of the tumor with microscopically intact resection margins (R0) is the single treatment option that has the strongest impact on prognosis.

ACC has a heterogeneous biological behavior ranging from less aggressive to rapidly progressing forms; however, our capability to predict the disease course remains imprecise at best, despite recent progress in prognostication. The disease course, and the prognosis of affected patients, is mainly determined by the high propensity of ACC to recur after an apparently radical extirpation, with a frequency up to 50–80% in some series. It has been said that ACC recurrence resets the tempo of disease, since life expectancy after the comeback of the tumor may be rather short and struggling. Therefore, preventing disease recurrence is a priority of the management strategy of ACC and this concept offers a well-founded rational for the institution of post-operative adjuvant therapy with a close follow-up for many years. Mitotane, an adrenolytic drug in use for decades, is the cornerstone of any therapeutic approach including adjuvant treatment. However, mitotane has a narrow therapeutic index, is burdened with frequent and disparate side effects, and needs careful dose tailoring and monitoring of blood concentrations.

ACC poses a unique challenge due to the combination of either oncological or endocrinological issues in any aspect of its management, from establishing the diagnosis to defining treatment; therefore, it is mandatory that ACC patients are managed by a multidisciplinary team at expert centers.

Case Presentation

A 26-year-old man was referred to our center after that an abdominal computed tomography (CT) scan showed a 12 cm heterogeneous mass in the right adrenal gland (Fig. 30.1). CT was ordered because the patient had complained of fatigue, loss of appetite with a 5 kg weight loss, and low-grade fever for 3 months, and a routine laboratory work-up revealed increased ESR (Erythrocyte Sedimentation Rate) and CRP (C-Reactive Protein). No comorbidity and no medication were reported. Physical exam did not reveal any remarkable feature and body mass index (BMI) was 22.5 kg/m^2.

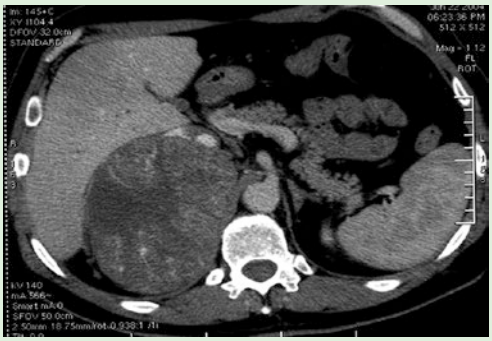

Fig. 30.1 CT scan (horizontal slice) showing the large right, inhomogeneous adrenal mass

In this case, which characteristics lead to suspect an ACC?

There are three important facts that need to be considered in this case:

1. Constitutive symptoms. Although classical malignancy-associated symptoms (weight loss, fatigue, anorexia, fever, and night sweats) are present only in a minority of cases, their presence is a warning bell. Most commonly, ACC presents with clinical features of hormone excess (50–60% of the cases), mainly hypercortisolism, which in women may be associated with signs of virilization, while pure hyperandrogenism is less frequent and estrogen or mineralocorticoid excess are rare. When signs of adrenal hormone excess are lacking, the clinical presentation often consists of symptoms due to an abdominal mass effect, such as nausea, vomiting, and back pain (30–40% of the cases). Interestingly, the serendipitous discovery of an ACC as an adrenal incidentaloma is increasingly frequent (10–15% of the cases), due to the widespread use of imaging procedures in clinics. In the present case, constitutive symptoms in a previously well-being young man should have raised the suspicion of a malignancy, although they are not specific for ACC. Therefore, the discovery of an adrenal mass may be considered as unexpected in this clinical scenario and this mass is an adrenal incidentaloma;
2. CT features of the mass. Although imaging cannot definitively prove a diagnosis of ACC, an adrenal malignancy can be ruled out when an adrenal mass appears homogenous and with low density at CT, considering a cut-off of ≤10 HU (Hounsfield Unit). Conversely, ACC should be suspected in case of an inhomogeneous mass with elevated density (due to low fat content). In addition, a large size enhances the probability of malignancy, especially when the mass is ≥4 cm, as other characteristics like intratumoral necrosis and irregular mass shape and borders;
3. The young age of the patient. The prevalence of adrenal masses increases with age and in elder subjects the occurrence of adrenal incidentalomas is frequent (up to 10%); conversely, an occasionally detected adrenal mass is an uncommon and disturbing finding in young subjects. Whether a benign adrenal adenoma is the leading cause of adrenal incidentalomas in the elderly, ACC is relatively more frequent in the young.

Is endocrine work-up required? Which tests?

There are several reasons to carry out a comprehensive endocrine work-up. Although the present patient did not show any sign of hypercortisolism or feminization, a mild autonomous adrenal hormone secretion, in particular a subtle cortisol excess, or a production of steroid precursors could not be ruled out without specific laboratory evaluation. The detection of an altered steroid pattern could confirm the diagnostic suspect of ACC, and the finding of a co-secretion of sexual hormones and cortisol virtually confirms that the adrenal mass is an ACC. An adrenocorticotropic hormone (ACTH)-independent hypercortisolism is a strong diagnostic element, although it is more frequently sustained by benign adrenal adenomas, and has prognostic value, because cortisol excess is tied to a worse outcome in ACC patients. At the same time, steroids may be markers of tumor remnant after surgery or recurrence during follow-up. The hormonal work-up must include a panel of different steroids including glucocorticoids, mineralocorticoids, androgens, and precursors to ascertain the adrenocortical origin of the tumor, but also metanephrines should be measured in urine or plasma to rule out a pheochromocytoma (Table 30.1). In fact, cross-sectional imaging cannot discriminate this tumor from ACC and a misdiagnosed pheochromocytoma may lead to life-threatening hypertensive crises (especially during invasive procedures and surgery).

Table 30.1 Hormonal work-up in case of suspected ACC

Type of secretion	Tests
Glucocorticoids	24-hour UFC Serum or salivary bedtime cortisol 1 mg DST (optional if the previous are altered) Plasma ACTH
Sexual steroids and steroid precursors	Serum DHEA-S Serum 17-OH-progesterone Serum androstenedione Serum testosterone (only in women) Serum 17-beta-estradiol (only in men and postmenopausal women)
Mineralocorticoids	Serum potassium Aldosterone/renin ratio (if arterial hypertension and/or hypokalemia)
Catecholamines	24-hour urinary fractionated (or plasma) metanephrines

ACTH adrenocorticotropic hormone, *DST* dexamethasone suppression test, *UFC* urinary free cortisol, *DHEA-S* dehydroepiandrosterone sulfate

Recently, it has been showed that high throughput methods (gas chromatography mass spectrometry, GC-MS, and liquid chromatography mass spectrometry tandem mass spectrometry, LC-MS) are able to recognize a particular steroid pattern even in tumors qualified as non-secreting with conventional methods. It has been demonstrated that GC-MS performed on 24-hour urine samples can recognize a distinct malignant steroid "fingerprint," which is able to pick up an ACC with sensitivity and specificity of 90%. Moreover, in plasma samples of ACC patients evaluated with LC-MS higher levels of 11-deoxycorticosterone, progesterone, 17-hydroxyprogesterone, 11-deoxycortisol, dehydroepiandrosterone (DHEA), DHEA sulfate (DHEA-S), and estradiol were detected, compared to patients with adrenocortical adenomas. Although these methods are not yet in clinical use, they appear as promising tools to discriminate efficiently benign from malignant adrenocortical tumors.

Is additional imaging needed? Which tests?

In any patient with suspected ACC, in addition to the abdominal cross-sectional imaging (CT or MRI), a chest CT is recommended for a complete staging of the disease that should inform the therapeutic approach (surgery, or chemotherapy in case

of unresectable or metastatic tumors). The thoraco-abdominal-pelvic imaging allows to investigate the most frequent sites of metastasis (lung and liver), while other tests are not routinely performed, because bone and brain metastasis are possible but rare at diagnosis. Although positron emission tomography with ^{18}F-2-deoxy-d-glucose (^{18}FDG-PET-CT) has been recently suggested as a second-line test, it is not routinely recommended in all patients, because of costs and limited availability in several countries.

Is tumor biopsy useful to confirm diagnosis?

No, adrenal biopsy has no role in the diagnostic process of ACC, because of low sensitivity (70%) and high risk of tumor dissemination and hemorrhage. Fine needle aspiration (FNA) biopsy could be considered in a non-secreting adrenal mass in a patient with history of extra-adrenal malignancy, to make the differential diagnosis between ACC and adrenal metastasis, or in case of widespread, inoperable ACC to secure a pathologic diagnosis.

What treatment?

Radical surgical removal of the tumor is the only possibility of cure for ACC and, when feasible with radical intent, surgery is always the first therapy. Although open surgery is considered the gold standard, laparoscopic adrenalectomy is increasingly used. The current recommendation is open surgery for tumors with evidence of local invasion, especially in case of large masses, while small tumors (≤6 cm) without signs of local invasion may be removed laparoscopically. The size cut-off for selecting laparoscopic adrenalectomy is matter of debate and experienced surgeons could remove laparoscopically even larger tumors. In any case, ACC surgery should be always performed by experienced surgeons in referral centers with a high operation volume.

Table 30.2 ENSAT staging system

	Tumor size	Lymph nodes	Distant metastasis
Stage 1	≤5 cm	Negative	Absent
Stage 2	>5 cm	Negative	Absent
Stage 3	Local invasion	Negative	Absent
	Any	Positive	Absent
Stage 4	Any	Any	Present

Patient underwent open surgery (en bloc tumor removal). Pathology report was ENSAT (European Network for the Study of Adrenal Tumors) tumor stage II, Ki67 25%, R0 margins. Should adjuvant mitotane therapy be considered?

Yes. In patients with localized disease, the risk of recurrence after surgery is strongly influenced by tumor stage, resection status, and Ki67 index. Tumor stage is currently assessed by using the ENSAT staging system (Table 30.2). Prognostication of ACC aims to stratify two different classes of localized ACC at different risk of recurrence. The low/moderate risk class is defined by the presence all of the following features: stage I–II ACC, R0 (microscopically free margins) surgery, and Ki67 ≤ 10%. The high-risk class is defined by at least one of these characteristics: stage III, or R1 (microscopically involved margins) /Rx (uncertain margins), or Ki67 > 10%. Although results from prospective randomized trials still lack, the positive effects of mitotane on recurrence-free survival in ACC patients with higher propensity to recur have been reported in several retrospective studies and have been confirmed in recent metanalyses. Therefore, adjuvant mitotane therapy is currently recommended for ACC at high risk of recurrence (Fig. 30.1). Mitotane should be started as soon as possible after surgery (ideally within 6 weeks, in any case not later than 3 months), according to the

biological concept of adjuvant therapy and also considering the latency to achieve blood mitotane concentrations with antitumoral efficacy.

What follow-up?

To allow the early detection of disease recurrence, patients must be followed with thoraco-abdominal-pelvic CT every 3 months for 2 years, then every 3–6 months for further 3 years. After 5 years, the risk of recurrence drops significantly, but is not zero. Therefore, continuation of follow-up appears as reasonable, with possible longer intervals between visits.

In addition to the radiological follow-up, a periodical biochemical assessment is useful either in patients with secreting tumors (steroids can be considered as biomarker of tumor recurrence after radical surgery) or in patients treated with mitotane to monitor the drug-related effects on endocrine functions, to permit adequate replacement therapy in case of need (Table 30.3). Primary adrenal insufficiency (hypoadrenalism) is an expected consequence of mitotane, and a key message is to use higher doses of steroids than those currently employed in Addison's disease due to the metabolization and inactivation of exogenous steroids by mitotane. Steroid under-replacement inflates mitotane-induced toxicity. Mineralocorticoid supplementation is not always required because the mitotane is less toxic for the zona glomerulosa. Levothyroxine replacement can be done in patients with a mitotane-induced reduction in FT4 levels, which usually occurs without a compensatory rise in TSH. In women, gonadal function is generally preserved with regular menstrual cycles, although in some cases ovarian cysts and menstrual disorders may occur. Conversely, testosterone replacement is frequently required in men, because mitotane inhibits testicular steroidogenesis. Finally, the monitoring of plasma mitotane levels is crucial, because this drug has a narrow therapeutic window, requiring blood concentrations >14 mg/L to be effective and <20 mg/L to avoid severe central neurological toxicity. Gastrointestinal adverse effects

Table 30.3 Management of mitotane-related unwanted effects

Effect	Parameters to monitor	Interval of monitoring	Treatment
Adrenal insufficiency	ACTH Morning cortisol Renin Electrolytes Blood pressure Body weight Well-being	Every 3 months[a]	Glucocorticoid replacement in all patients treated with mitotane, using hydrocortisone or cortisone acetate; in patients with symptoms and signs of insufficient mineralocorticoid activity (hyperkalemia, hyponatremia, and hypotension) add fludrocortisone.
Deranged thyroid function (total T4 ↓, free T4 ↓, TSH ↓)	TSH FT4	Every 3 months	Replacement therapy with L-thyroxine in patients with central hypothyroidism
Primary hypogonadism (in men)	Testosterone SHBG	Every 3 months[a]	Testosterone supplementation in patients with low testosterone and symptoms of hypogonadism
Dyslipidemia	Total cholesterol HDL cholesterol Triglycerides	Every 3 months	In selected cases with good life expectancy, statin therapy (preferably rosuvastatine or pravastatine)

[a]Sooner if clinically indicated
SHBG sex hormone-binding globulin, *HDL* high-density liprotein

are common also in patients with plasma mitotane concentration in range, requiring symptomatic therapy such as antiemetic and anti-diarrheal drugs. Conversely, significant liver toxicity (characterized by marked increase in transaminases and bilirubin) is rare, while elevation in gamma-glutamyl transferase (GGT) levels is a universal finding that usually comes without any clinical consequence. To tackle mitotane toxicity, it is useful to reduce the dose or, in case of severe side effects, to temporarily stop the drug. In conclusion, an important role of the clinician is to motivate patients to maintain adherence to treatment, adjust mitotane dose in relation to side effects and drug levels, put in place supportive therapies (hormonal replacement and symptomatic treatments) whenever indicated. Therefore, a specific expertise and great availability to maintain a strict relationship with the patients are fundamental to deal with mitotane treatment and its unwanted effects.

How long should the patient be treated?

The optimal duration of adjuvant mitotane treatment is presently unknown, because definitive evidence is not available. In current practice, patients should be kept on mitotane for at least for 2 years; however, we recommend longer treatment spans (up to 4–5 years) in patients with good compliance and unfavorable prognostic factors. After mitotane is discontinued, recovery of adrenal function is not immediate; conversely, a comeback to normal requires a median period of 2.7 years but it may be as long as 8 years in some cases. In about 20% of cases, a complete recovery is never attained or patients are unable to tolerate glucocorticoid withdrawal despite apparently normal hormonal tests.

Tips

- The reader is advised to read the chapters on Adrenal Incidentaloma and Adrenal Cushing's Syndrome (in this Section on Diseases of the Adrenal).

Take Home Messages

- Adrenal carcinoma is a rare endocrine tumor that is usually tied to poor prognosis.
- The diagnosis includes hormonal work-up (ACTH, a complete steroid panel) and imaging assessment (abdominal and chest CT scan).
- Surgery (en bloc tumor resection) is the only treatment offering a concrete possibility of cure.
- Adjuvant treatment with mitotane is justified in patients at high risk of recurrence.
- Treatment with mitotane requires careful management of treated patients to deal with the unwanted effects of the drug, to promote compliance, and to evaluate drug activity.
- The management of both oncological and endocrinological issues, including the challenges posed by treatment, entails that ACC patient care should be provided in reference centers, by an expert and multidisciplinary team.

Suggested Reading

1. Arlt W, Biehl M, Taylor AE, Hahner S, Libé R, Hughes BA, Schneider P, Smith DJ, Stiekema H, Krone N, Porfiri E, Opocher G, Bertherat J, Mantero F, Allolio B, Terzolo M, Nightingale P, Shackleton CH, Bertagna X, Fassnacht M, Stewart PM. Urine steroid metabolomics as a biomarker tool for detecting malignancy in adrenal tumors. J Clin Endocrinol Metab. 2011;96:3775–84. https://doi.org/10.1210/jc.2011-1565.
2. Fassnacht M, Arlt W, Bancos I, Dralle H, Newell-Price J, Sahdev A, Tabarin A, Terzolo M, Tsagarakis S, Dekkers OM. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2016;175:G1–G34. https://doi.org/10.1530/EJE-16-0467.
3. Fassnacht M, Dekkers OM, Else T, Baudin E, Berruti A, de Krijger R, Haak HR, Mihai R, Assie G, Terzolo M. European Society of Endocrinology Clinical Practice Guidelines on the management of adrenocortical carcinoma in adults, in collaboration with the European

Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2018;179:G1–G46. https://doi.org/10.1530/EJE-18-0608.
4. Poirier J, Gagnon N, Terzolo M, Puglisi S, Ghorayeb NE, Calabrese A, Lacroix A, Bourdeau I. Recovery of adrenal insufficiency is frequent after adjuvant mitotane therapy in patients with adrenocortical carcinoma. Cancers. 2020;12:639. https://doi.org/10.3390/cancers12030639.
5. Puglisi S, Calabrese A, Basile V, Pia A, Reimondo G, Perotti P, Terzolo M. New perspectives for mitotane treatment of adrenocortical carcinoma. Best Pract Res Clin Endocrinol Metab. 2020;34:101415. https://doi.org/10.1016/j.beem.2020.101415.
6. Schweitzer S, Kunz M, Kurlbaum M, Vey J, Kendl S, Deutschbein T, Hahner S, Fassnacht M, Dandekar T, Kroiss M. Plasma steroid metabolome profiling for the diagnosis of adrenocortical carcinoma. Eur J Endocrinol. 2019;180:117–25. https://doi.org/10.1530/EJE-18-0782.
7. Tang Y, Liu Z, Zou Z, Liang J, Lu Y, Zhu Y. Benefits of adjuvant mitotane after resection of adrenocortical carcinoma: a systematic review and meta-analysis. Biomed Res Int. 2018;2018:9362108. https://doi.org/10.1155/2018/9362108.
8. Terzolo M, Daffara F, Ardito A, Zaggia B, Basile V, Ferrari L, Berruti A. Management of adrenal cancer: a 2013 update. J Endocrinol Investig. 2014;37:207–17. https://doi.org/10.1007/s40618-013-0049-2.

Addison's Disease and Autoimmune Polyendocrine Syndrome Type 2

Abel Decmann and Peter Igaz

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_31

Opening

Primary adrenal insufficiency (Addison's disease) is most commonly of autoimmune origin that often forms part of the autoimmune polyendocrine syndrome (APS) type 2 in adults.

Definition of the Disease

Addison's disease or primary adrenal insufficiency (PAI) is a rare disease with a prevalence of 144–221 cases per million population. Addison's disease results in adrenal hormone deficiency that affects all three layers of the adrenal cortex. PAI can be caused by a number of etiological factors. Nowadays, autoimmune adrenalitis is responsible for more than 80% of all cases in developed countries. The second most common etiology of PAI is represented by infections destructing the adrenal tissue (tuberculosis, HIV infection, and fungal infections). Other etiological factors are more infrequent such as adrenal hemorrhage, sepsis, surgery, drugs, or metastasis (Table 31.1). Autoimmune adrenalitis can be part of the autoimmune polyendocrine syndromes (APS) that affect several endocrine (and also non-endocrine) organs. Whereas APS type 1 (APS-1) is a very rare monogenic disease typically diagnosed in children, APS type 2 (APS-2) is more frequent, polygenic, and characteristic for adults. The most characteristic diseases in APS-2 include Addison's disease, thyroid disease (mostly hypothyroidism, but hyperthyroidism might also occur), and type 1 (autoimmune) diabetes mellitus.

The autoimmune adrenalitis usually affects the zona glomerulosa first leading to low aldosterone and elevated renin activity. Then, the destruction of the zona fasciculata manifests itself in decreased basal cortisol and elevated adrenocorticotropic hormone (ACTH) levels. In adrenal insufficiency, any kind of stress can cause a rapid decompensation of the disease, leading to adrenal crisis, coma, or death. Adrenal crisis is a shock situation caused by sodium depletion and decreased vasoconstrictor response due to mineralocorticoid-deficiency and by decreased vascular responsiveness to angiotensin II and noradrenaline occurring in glucocorticoid deficiency.

Table 31.1 Major causes of Addison's disease

Autoimmune	Isolated autoimmune adrenalitis Autoimmune polyendocrine syndromes type 1 and 2
Infectious	Tuberculosis HIV infection Fungal infection (histoplasmosis and paracoccidio idomycosis) African trypanosomiasis
Tumor	Cancer metastases (lung, breast, and colon) Lymphoma
Adrenal hemorrhage/ infarction	Trauma and anticoagulant therapy Waterhouse-Friderichsen syndrome

Table 31.1 (continued)

Drugs	Inhibitors of steroid biosynthesis (ketoconazole[a], aminoglutethimide, and mitotane) Antimycotic drugs (fluconazole) Antiepileptic drugs (barbiturates and phenytoin)
Infiltrative diseases	For example, hemochromatosis and adrenoleukodystrophy

Waterhouse-Friderichsen syndrome is bilateral adrenal hemorrhage caused by sepsis (typically by *Neisseria meningitidis* (meningococcemia), but sepsis by other pathogens, for example, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Escherichia coli* were also reported). Hemochromatosis is one of the most frequent inherited diseases (caused by several genes and inherited as autosomal traits) that results in iron deposition in various organs, rarely in the adrenal. Adrenoleukodystrophy is a rare X-linked inherited disease that is the most common peroxisomal disorder due to the deposition of very long fatty acids mainly in the central nervous system and the adrenals

[a]Ketoconazole was originally an antimycotic drug, but later was introduced as a treatment option for hypercortisolism due to its steroid inhibitory side effects (see ► Chap. 27 on adrenal Cushing's syndrome)

Case Presentation

A 47-year-old lady was referred to our center with symptoms of fatigue and vomiting. Initial evaluation of the patient showed hyponatremia (124 mmol/L – normal range: 135–145), hypotension, and skin hyperpigmentation. Three months earlier the patient was diagnosed with hypothyroidism and thyroid hormone replacement with daily 75 μg L-thyroxine was introduced. Chest X-ray, gastroscopy, colonoscopy, abdominal ultrasound, and abdominal-pelvic computed tomography showed nothing remarkable.

Which of these symptoms could be suggestive of Addison's disease?

The most typical symptoms of Addison's disease include fatigue (80–90%), weight loss (60–70%), nausea and vomiting (50–60%), and pains (abdominal, muscle, and joint). Weight loss is mostly due to anorexia, but dehydration might also be relevant. Salt craving is observed in 40–60% of patients. Women often experience menstrual irregularities, decreased libido, and loss of pubic or axillary hair. The patient complained of fatigue, nausea, and vomiting that correspond to the typical symptoms.

What kind of signs should be looked for?

Skin and mucosal hyperpigmentation is a characteristic sign in Addison's disease that is seen in about 40–70% of patients. Hyperpigmentation can be generalized (Fig. 31.1), but it is often most conspicuous at the palmar creases and gingiva. Skin surfaces exposed to sun and to pressures (e.g., elbow) are often affected. Vitiligo resulting in hypopigmented patches of autoimmune origin is often observed along with hyperpigmentation in Addison's disease patients of autoimmune origin.

Postural hypotension is a typical sign (Schellong's sign) (in about 55–70% of patients): following a 5 min long supine rest, the patient stands up, and there is a drop of >20 mmHg in the systolic, or >10 mmHg in the diastolic blood pressure.

Dizziness and even syncope are often observed.

Regarding common laboratory alterations, hyponatremia is most common (70–80%). Hyperkalemia (normal serum potassium: 3.5–5.0 mmol/L) is observed in 30–40% of patients. Some patients exhibit severe hyperkalemia (serum K^+ > 7.0 mmol/L), but it is important to note that renal function is normal. Hypoglycemia may also occur. Eosinophilia and anemia can also

Fig. 31.1 (**a**) An Addison's patient at diagnosis, and (**b**) 6 months after the initiation of glucocorticoid replacement. Note the disappearance of diffuse hyperpigmentation following successful therapy

be rarely observed. (Many decades ago, before the advent of hormone measurements, eosinophilia was considered as a useful sign for the diagnosis of Addison's disease, whereas the lack of eosinophils in peripheral blood smears was used for the diagnosis of hypercortisolism.)

What is the etiology of hyperpigmentation?

Due to the lack of cortisol production, pituitary ACTH (adrenocorticotropin) release is increased as the negative feedback regulation exerted by cortisol is not working. ACTH has melanocyte stimulating hormone (MSH) activity and its high concentration results in hyperpigmentation.

What kind of other diseases are associated with ACTH-mediated hyperpigmentation?

High ACTH levels leading to hyperpigmentation can be seen in ectopic ACTH syndrome and Nelson syndrome, as well. Ectopic ACTH syndrome is a form of hypercortisolism (Cushing's syndrome) (▶ Chap. 27) that often results in very high ACTH levels. *Nelson syndrome* is rarely observed in patients suffering from pituitary Cushing's disease that is cured with bilateral adrenalectomy leaving the ACTH-source of the pituitary back in the patient. The fallout of cortisol due to adrenalectomy eliminates the negative feedback on the pituitary, and the ACTH-producing pituitary adenoma can grow aggressively and produce excessive amounts of ACTH.

What is an adrenal crisis (acute adrenal insufficiency)?

Adrenal crisis is a shock situation due to the lack of both mineralocorticoid and glucocorticoid hormones. Similar to chronic adrenal insufficiency, fatigue and weakness, anorexia, nausea, and vomiting are also often observed. Patients might have fever, and intensive abdominal pains

that might even mimic an acute abdominal catastrophe. Adrenal crisis is most often precipitated in patients with chronic Addison's disease by a variety of stressors (such as infections, trauma, and surgery). To prevent adrenal crisis, glucocorticoid substitution doses should be increased in stress situations (see later). Very rarely, acute adrenal crisis might develop due to the rapid destruction of the adrenal glands that is typically observed in adrenal hemorrhage/infarction (e.g., by Waterhouse-Friderichsen syndrome induced typically by meningococcal sepsis) (Table 31.1).

What are the major differences between primary and secondary adrenal insufficiency?

Whereas primary adrenal insufficiency affects all layers of the adrenal gland and therefore results in both glucocorticoid and mineralocorticoid deficiency (and also lack of adrenal androgens), secondary adrenal insufficiency due to pituitary ACTH deficiency (and the rare tertiary adrenal insufficiency due to hypothalamic CRH (corticotropin releasing hormone) defects) results only in glucocorticoid deficiency leaving the mineralocorticoid axis intact. The secretion of mineralocorticoids is mostly regulated by factors other than ACTH (e.g., angiotensin II and serum potassium), and therefore ACTH deficiency does not considerably affect the secretion of aldosterone. The clinical consequence of this is represented by the lack of hyperkalemia in secondary (tertiary) adrenal insufficiency, and certainly there is also no hyperpigmentation in ACTH deficiency. Hyponatremia, however, is also typical for secondary adrenal insufficiency.

How should the diagnosis of Addison's disease be established?

The hormonal diagnosis is relatively easy. A low morning serum cortisol and a highly elevated level of plasma ACTH is a typical scenario. If the morning cortisol is below 3 μg/dl (80 nmol/L), it is highly suggestive of adrenal insufficiency (both primary and secondary). Aldosterone is also low and renin is concomitantly high. *The first hormone measurements of the patient displayed a low morning cortisol (2.3 μg/dL (normal range: 8.0–25.0) and high plasma ACTH 943.3 pg/mL (normal range: 7.2–63.3)). Dehydroepiandrosterone sulfate (DHEAS) was actually undetectable (<2.0 μg/dL, normal range: 130.0–330.0).*

A short (large dose) ACTH-stimulation test (tetracosactid and cosyntropin) is the standard test, when 250 μg tetracosactid is injected intravenously and cortisol is measured 30 or 60 min. thereafter. Cortisol levels increase above 20 μg/dl (550 nmol/L) in normal individuals.

Can the ACTH-stimulation test be used for the diagnosis of secondary adrenal insufficiency?

As the adrenal atrophies in ACTH deficiency, the ACTH-stimulation test is also helpful in the diagnosis in secondary adrenal insufficiency. However, the development of adrenal atrophy takes several weeks after the cessation of ACTH-production (e.g., pituitary surgery or hemorrhage), and therefore the test is only useful after this period. The standard, 250 μg tetracosactid (cosyntropin) test includes a very high dose, and its sensitivity is limited for mild secondary adrenal insufficiency. A low dose (1 μg tetracosactid) ACTH-test has also been developed primarily for secondary adrenal insufficiency, but it is not universally accepted, as its results are variable and the preparation is not commercially available.

How does the clinical evolution of Addison's disease look like?

Like type 1 diabetes mellitus, the progression of Addison's disease of autoimmune origin is slow and there are hormonal alterations in the preclinical stage already that usually remain undiagnosed. The progression of Addison's disease can be divided into four stages. First, the zona

glomerulosa is affected and the secretion of aldosterone is compromised along with elevated levels of renin. The second stage is characterized by decreased responsiveness of cortisol to ACTH-stimulation. In the third stage, ACTH levels are elevated, but the morning cortisol is still normal. The fourth stage is the overt disease with low morning cortisol and increased ACTH levels.

What kind of investigations should be performed to clarify the etiology of Addison's disease?

The autoimmune background of adrenal insufficiency can be investigated by various antibodies to steroidogenic enzymes (e.g., 21-hydroxylase and 17-hydroxylase/17,20 lyase). Imaging of the adrenals can also be helpful as adrenals tend to show atrophy in autoimmune adrenalitis, whereas adrenals can be enlarged in cases associated with, for example, tuberculosis, metastasis, infiltrative diseases, and hemorrhage. Tuberculotic adrenals often show calcification.

Which hormonal alteration could indicate the autoimmune origin of the disease in our case?

The patient has already been treated for hypothyroidism before the diagnosis of Addison's disease. The combination of Addison's disease and hypothyroidism is a common scenario that can be characteristic for patients with autoimmune polyendocrine syndrome type 2.

What are the major features of autoimmune polyendocrine syndrome type 2?

Our patient was diagnosed with hypothyroidism before the appearance of Addison's disease, and the ultrasound morphology of her thyroid was characteristic for Hashimoto's thyroiditis. This constellation is typical for type 2 autoimmune polyendocrine syndrome (APS-2) and was originally called the *Schmidt syndrome*. APS-2 is a polygenic disease that is more common in women than in men and is usually diagnosed in the ages between 20 and 40 years. Its prevalence ranges between 1.4 and 4.5/100.000. The major manifestations of APS-2 include Addison's disease, autoimmune thyroid disease (mostly hypothyroidism of autoimmune origin (Hashimoto's thyroiditis), but hyperthyroidism related to Graves' disease might also occur) and type 1 diabetes mellitus. The combination of Addison's disease, autoimmune thyroid disease and type 1 diabetes mellitus was called *Carpenter syndrome*. The manifestations of APS-2 syndrome are presented in Table 31.2. In contrast with the APS-1 syndrome, hypoparathyroidism is not a feature of this disease. Several non-endocrine autoimmune features have been described as well.

Table 31.2 Manifestations of the autoimmune polyendocrine syndrome type 2 (APS-2)

Manifestation	Prevalence
Addison's disease	100%
Autoimmune thyroid disease (Hashimoto's thyroiditis, hypothyroidism, and Graves' disease)	70–80%
Type 1 diabetes mellitus	30–50%
Primary (hypergonadotropic) hypogonadism (ovarian failure)[a]	5–50%
Vitiligo	4–10%
Alopecia	1–5%
Chronic autoimmune hepatitis	<5%
Other non-endocrine autoimmune manifestations (pernicious anemia, alopecia, Sjögren's syndrome, rheumatoid arthritis, myasthenia gravis, immune thrombocytopenia, celiac disease, and stiff man syndrome)	Variable, usually rare (<1%)

[a]Testicular failure is much more uncommon than ovarian failure

What kind of autoantibodies can be found in APS-2 syndrome patients?

Apart from antibodies to steroidogenic enzymes causing autoimmune adrenalitis, antibodies to thyroid antigens (thyroglobulin, thyroid peroxidase, and thyroid stimulating hormone in Graves' disease) and antibodies to pancreatic antigens (insulin, glutamic acid decarboxylase, islet cell, and protein tyrosine phosphatase) can also be found. The anti-thyroid peroxidase (anti-TPO) level was 600 IU/mL in our patient (normal range 0–63 IU/mL).

Antibodies to these antigens can be detected in many patients suffering from Addison's disease even without overt clinical manifestations. Such subclinical forms are important to recognize, as these patients should be regularly followed-up for diagnosing the other manifestations on time.

What are the major features of autoimmune polyendocrine syndrome type 1?

APS-1 is a rare disease inherited as an autosomal recessive trait that is caused by mutations of the *AIRE* (autoimmune regulator) gene. *AIRE* encodes a transcription factor involved in the regulation of expression of antigens by the thymic medullary epithelial cells. Defects of *AIRE* disturb the selection of thymocytes and thereby autoreactive T-cells survive in these patients. The major clinical features of APS-1 include mucocutaneous candidiasis, ectodermal dysplasia (enamel hypoplasia), and primary hypoparathyroidism as first manifestations, and later Addison's disease develops. Primary hypogonadism (mostly ovarian) is also a typical feature along with enteropathy (chronic diarrhea or constipation). In contrast to APS-2, thyroid autoimmunity and diabetes mellitus are uncommon features of the disease.

Antibodies to the calcium sensor protein are responsible for a portion of autoimmune hypoparathyroidism in APS-1, and the other antibodies against endocrine organs overlap with those found in APS-2. The most prevalent antibodies in APS-1 are those against interferons (interferon α and ω).

What kind of other forms of autoimmune endocrine diseases could be mentioned?

According to the classification of Neufeld and Blizzard (1980), categories of types 3 and 4 autoimmune polyendocrine syndromes (APS-3 and APS-4) have also been established, but these are not so well defined as APS-1 and APS-2. APS-3 is the combination of autoimmune thyroid disease and other autoimmune diseases (often type 1 diabetes mellitus) excluding Addison's disease, hypoparathyroidism, and candidiasis (i.e., the features of APS-1). APS-4 is a very broad category including combinations of organ-specific autoimmune diseases that do not fall in any other APS category.

POEMS syndrome is a rare disease belonging to the group of monoclonal plasma cell disorders, but it has also endocrine manifestations that are shown by the "E" letter in its abbreviation (POEMS: polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes). About two thirds of POEMS syndrome patients display endocrine abnormalities, mostly primary hypogonadism and hypothyroidism, but rarely adrenal insufficiency is also observed.

Among the other very rare syndromes associated with multiple autoimmune endocrine manifestations, the IPEX syndrome (immune dysregulation, polyendocrinopathy, endocrinopathy, X-linked) can be mentioned that is a severe monogenic disease mostly lethal in childhood associated with mutations of the transcription factor FOXP3. The DIDMOAD syndrome (Diabetes insipidus, diabetes mellitus, optic atrophy, and deafness, otherwise called the Wolfram syndrome) and the mitochondrial Kearns-Sayre syndrome also include autoimmune endocrine manifestations.

Can an autoimmune polyendocrine syndrome be of iatrogenic origin?

Due to the increasing use of potent immune checkpoint inhibitors in the treatment protocols of various cancers, a growing prevalence of autoimmune side effects is observed. Cytotoxic T lymphocyte associated-4 (CTLA-4) and programmed cell death protein 1 (PD-1) inhibitors can induce autoimmune reactions in many endocrine organs including the pituitary (► Chap. 8 on Hypophysitis), thyroid and adrenals, and thus features of autoimmune polyendocrinopathies can develop.

How should Addison's disease be treated?

Hydrocortisone substitution is the mainstay of treatment. Hydrocortisone is the same molecule as cortisol secreted by the adrenal cortex. The daily production of cortisol is about 15–25 mg, and this is given in two or three divided doses. The largest dose (2/3 of the daily dose) should be given in the morning to resemble normal daily secretion (e.g., 10 mg in the morning and 5 mg in the afternoon). However, the normal diurnal rhythm of glucocorticoids is difficult to replicate by this way, and some patients complain about weakness, headache, and nausea in the morning. A once daily, dual release hydrocortisone preparation is already available on the market to overcome these problems, but its utility is variable. Some patients benefit from longer acting steroids (e.g., prednisolone or dexamethasone) given in the evening. The daily dose of prednisolone and dexamethasone corresponding to 30 mg of hydrocortisone is 5 mg and 1 mg, respectively.

In addition to glucocorticoid substitution, mineralocorticoids should also be given. The daily dose of the synthetic steroid with mineralocorticoid activity, fludrocortisone is 0.05–1 mg given in two doses.

In women, administration of DHEA (25–50 mg daily) can also be helpful to improve mood and libido.

How can the treatment response be monitored?

Plasma ACTH is used to monitor glucocorticoid, whereas renin (activity or concentration) for mineralocorticoid substitution. However, it is most important to follow-up the patients clinically, as some patients don't reach normal ACTH levels, but feel well. Excessive substitution with glucocorticoids can lead to Cushing's syndrome (► Chaps. 3 and 27).

What is the difference in the treatment of primary and secondary adrenal insufficiency?

The glucocorticoid doses needed are usually smaller in secondary than in primary adrenal insufficiency. Patients with secondary adrenal insufficiency (hypopituitarism) do not need mineralocorticoid substitution.

What is the therapeutic consequence of concomitant hypothyroidism and adrenal insufficiency? What should be treated first?

APS-2 patients often have both hypothyroidism and Addison's disease (as in our case), and deficiency for ACTH and TSH can also occur together in hypopituitarism (secondary adrenal insufficiency and secondary hypothyroidism). It is most important to note that if there is a suspicion for adrenal insufficiency, thyroid substitution should not be started first as the metabolism-promoting action of thyroid hormones could promote the degradation of cortisol and therefore could precipitate an acute adrenal insufficiency. Thyroid hormones should only be given after the treatment with glucocorticoids has already been initiated.

What should be done during acute situations to prevent adrenal crisis?

The normal adrenal cortex can considerably increase the production of glucocorticoids in stress situations (e.g., infection,

trauma, and surgery). To prevent adrenal crisis, patients should be educated to increase the doses of hydrocortisone two- to three-fold if they experience symptoms suggestive of adrenal insufficiency (dizziness, malaise, and fever). If the patient is unable to take oral medication, 100 mg hydrocortisone can be self-injected intramuscularly (in patients taking no anticoagulants, as intramuscular injection in anticoagulated patients could lead to severe hematomas). Parenteral hydrocortisone should be given to patients having surgical intervention, and the dose depends on the type of surgery. For minor surgical interventions (e.g., in local anesthesia), 25 mg hydrocortisone could be sufficient on the day of the operation and then returning to the standard peroral regimen the next day. For more serious operations (e.g., appendectomy), daily 50–75 mg hydrocortisone should be given on the day on the intervention and the day thereafter, then returning to standard regimen. Operations associated with severe stress (e.g., neurosurgical or long abdominal intervention) require higher doses, for example, 3–4 × 50 mg hydrocortisone in infusion, but doses can go up to 3–4 × 100 mg given in parenteral infusions. The dose should then be tapered gradually during the postoperative days. By so high doses of hydrocortisone, mineralocorticoid administration is no longer necessary.

How should an adrenal crisis be managed?

Fluid resuscitation and intravenous glucocorticoids represent the mainstay of treatment. Patients often display severe hyponatremia and hyperkalemia, therefore potassium-free isotonic infusions should be given. 100 mg hydrocortisone should be first given in an intravenous bolus or in infusion, and then 3–4 × 50 mg hydrocortisone in infusion. If the patient displays fever, antibiotics are also frequently given, despite observations that adrenal crisis alone can lead to fever even without infection. If the diagnosis of adrenal insufficiency has not been known before, blood samples for cortisol and ACTH levels should be taken before administering hydrocortisone. If hydrocortisone is not available, other steroids, for example, intravenous methylprednisolone and dexamethasone can also be given (20 mg methylprednisolone and 4 mg dexamethasone correspond to approximately 100 mg hydrocortisone).

Tips

The reader is advised to read the Chapter on hypopituitarism (► Chap. 6), hypophysitis (► Chap. 8), and ► Chap. 11 (hypothyroidism and Hashimoto thyroiditis).

Take Home Messages

- Primary adrenal insufficiency (Addison's disease) is associated with deficiency for both glucocorticoids and mineralocorticoids.
- Addison's disease is most frequently of autoimmune origin and is often observed as a part of autoimmune polyendocrine syndrome type 2. Major features of autoimmune polyendocrine syndrome type 2 include Addison's disease, autoimmune thyroid disease (mostly thyroiditis and hypothyroidism) and type 1 diabetes mellitus.
- Major symptoms and signs include fatigue, malaise, muscle and joint pains, hypotension, hyperpigmentation, hyponatremia, hyperkalemia, and hypoglycemia.
- Adrenal crisis (acute adrenal insufficiency) is a life-threatening condition associated with severe fatigue, malaise, vomiting, hypotension, fever, and abdominal pains.
- Hormonal diagnosis is based on low morning cortisol and high plasma ACTH, and subnormal stimulation by the short ACTH-stimulation test.
- The mainstay of treatment in chronic cases is glucocorticoid (hydrocortisone)

and mineralocorticoid (fludrocortisone) substitution.
- Adrenal crisis is treated with parenteral hydrocortisone (or other steroid, e.g., methylprednisolone or dexamethasone) and infusions.
- Glucocorticoid doses should be increased in stress situations (e.g., infection, trauma, and surgical intervention) to prevent adrenal crisis.

Suggested Reading

1. Betterle C, Dal Pra C, Mantero F, Zanchetta R. Autoimmune adrenal insufficiency and autoimmune polyendocrine syndromes: autoantibodies, autoantigens, and their applicability in diagnosis and disease prediction. Endocr Rev. 2002;23(3):327–64. https://doi.org/10.1210/edrv.23.3.0466.
2. Betterle C, Scarpa R, Garelli S, Morlin L, Lazzarotto F, Presotto F, Coco G, Masiero S, Parolo A, Albergoni MP, Favero R, Barollo S, Salva M, Basso D, Chen S, Rees Smith B, Furmaniak J, Mantero F. Addison's disease: a survey on 633 patients in Padova. Eur J Endocrinol. 2013;169(6):773–84. https://doi.org/10.1530/eje-13-0528.
3. Betterle C, Presotto F, Furmaniak J. Epidemiology, pathogenesis, and diagnosis of Addison's disease in adults. J Endocrinol Investig. 2019;42(12):1407–33. https://doi.org/10.1007/s40618-019-01079-6.
4. Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, Husebye ES, Merke DP, Murad MH, Stratakis CA, Torpy DJ. Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2016;101(2):364–89. https://doi.org/10.1210/jc.2015-1710.
5. Dispenzieri A. POEMS syndrome: 2019 update on diagnosis, risk-stratification, and management. Am J Hematol. 2019;94(7):812–27. https://doi.org/10.1002/ajh.25495.
6. Erichsen MM, Lovas K, Skinningsrud B, Wolff AB, Undlien DE, Svartberg J, Fougner KJ, Berg TJ, Bollerslev J, Mella B, Carlson JA, Erlich H, Husebye ES. Clinical, immunological, and genetic features of autoimmune primary adrenal insufficiency: observations from a Norwegian registry. J Clin Endocrinol Metab. 2009;94(12):4882–90. https://doi.org/10.1210/jc.2009-1368.
7. Frommer L, Kahaly GJ. Autoimmune Polyendocrinopathy. J Clin Endocrinol Metab. 2019;104(10):4769–82. https://doi.org/10.1210/jc.2019-00602.
8. Husebye ES, Anderson MS, Kampe O. Autoimmune Polyendocrine Syndromes. N Engl J Med. 2018;378(12):1132–41. https://doi.org/10.1056/NEJMra1713301.
9. Leshin M. Polyglandular autoimmune syndromes. Am J Med Sci. 1985;290(2):77–88. https://doi.org/10.1097/00000441-198508000-00007.
10. Neufeld M, Maclaren N, Blizzard R. Autoimmune polyglandular syndromes. Pediatr Ann. 1980;9(4):154–62.
11. Neufeld M, Maclaren NK, Blizzard RM. Two types of autoimmune Addison's disease associated with different polyglandular autoimmune (PGA) syndromes. Medicine. 1981;60(5):355–62. https://doi.org/10.1097/00005792-198109000-00003.
12. Neary N, Nieman L. Adrenal insufficiency: etiology, diagnosis and treatment. Curr Opin Endocrinol Diabetes Obes. 2010;17(3):217–23. https://doi.org/10.1097/MED.0b013e328338f608.

Salt Wasting 21-Hydroxylase Deficiency

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Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_32

Opening

Congenital adrenal hyperplasia (CAH) is a group of inherited disorders of cortisol biosynthesis in the adrenal cortex. 21-Hydroxylase deficiency (21-OHD) is the most common form of CAH. 21-OHD is further divided into classical and non-classical forms (NCAH). Most classical CAH patients have the salt wasting type of CAH (SW-CAH). The complete inability to produce cortisol and aldosterone in SW-CAH results in life-threatening salt wasting and adrenal crisis in the first few weeks of life without treatment, therefore 21-OHD is part of most neonatal screening programs. Alterations in adrenal hormone synthesis result in early androgen excess causing virilization symptoms in females both in utero and later in life. SW-CAH patients need lifelong hormone replacement therapy and close monitoring for not only endocrine but also numerous other health-related problems.

Definition of the Disease

Congenital adrenal hyperplasia is a group of genetic disorders affecting enzymes and proteins participating in cortisol biosynthesis in the adrenal cortex. The majority of cases, 95% is caused by mutation or deletion of the gene encoding the 21-hydroxylase enzyme. 21-Hydroxylase participates in both aldosterone and cortisol biosynthesis (◘ Fig. 32.1). The defect of the 21-hydroxylase enzyme activity can be complete or incomplete, representing a continuous spectrum. CAH owing to 21-OHD is divided into two categories based on clinical presentation: classical and non-classical CAH. Classical CAH is further divided into salt wasting and simple virilizing forms based on the presence or absence of clinical mineralocorticoid deficiency.

The incidence of classical 21-OHD is 1:13,000–15,000 live births.

The deficiency of the 21-OHD enzyme results from a genetic defect of the *CYP21A2* gene on chromosome 6. It is inherited as an autosomal recessive trait and specific mutations are corresponding to different clinical manifestations and severity of disease; therefore the male to female ratio is equal if a neonatal screening program is in effect; however, without neonatal screening, some male SW-CAH patients are missed based on the lack of ambiguous genitalia at birth and might die unrecognized in an early salt wasting crisis.

The inability to produce appropriate amounts of cortisol disables the negative feedback on the hypothalamic-pituitary system, leading to increased adrenocorticotropic hormone (ACTH) secretion. The high ACTH levels continuously stimulate the adrenal cortex, leading to adrenal hyperplasia and an overstimulation of hormone production. However, despite the supraphysiologic stimuli, appropriate cortisol production cannot be achieved, and intermediate products of cortisol biosynthesis are diverted to androgen biosynthesis resulting in androgen excess and virilization symptoms.

The adrenal cortex under physiological conditions produces 1000-fold more cortisol than aldosterone. Therefore, in case of an incomplete loss of 21-hydroxylase activity, mineralocorticoid production can be maintained to avoid clinical manifestations of salt loss: hyponatremia, hyperkalemia, hypovolemia, vomiting, failure to thrive, seizure, and shock. In case of complete or nearly complete loss of 21-hydroxylase activity (less than 2%) salt wasting occurs (SW-CAH). Incomplete loss of 21-hydroxylase activity (more than 2%) causes SV-CAH or non-classical CAH (NCAH).

The main clinical symptoms of untreated SW-CAH in the neonatal period is failure to thrive, hypovolemia, hyponatremia, hyperkalemia, hypoglycemia, vomiting, increased intracranial pressure, seizures and shock in both genders, ambiguous genitalia in females, and mildly hyperpigmented and wrinkled scrotum in males. Later several salt wasting episodes

can occur especially in childhood related to intercurrent infections. Undertreatment leads to adrenarche and pubarche praecox, which if chronic might induce central precocious pubarche. Problems related to mineralocorticoid deficiency decrease with age, however, lifelong hormonal replacement is required with combination of mineralocorticoid and glucocorticoid in addition to sodium chloride replacement in childhood. Metabolic complications and subfertility are common problems among adult CAH patients. (For a more detailed discussion, see the SV-CAH chapter (► Chap. 33).)

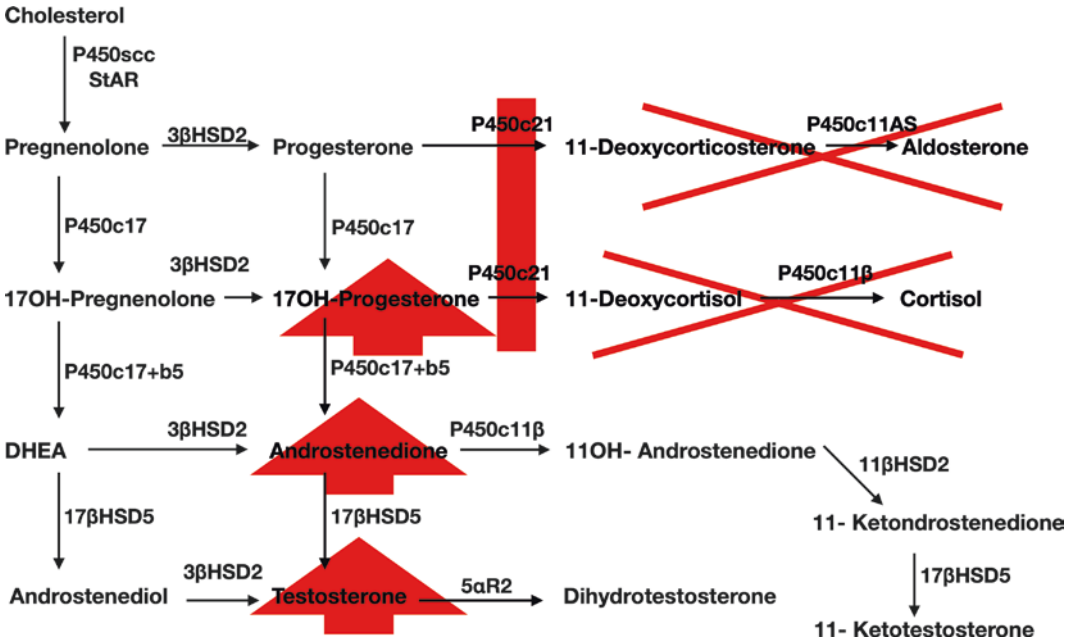

Fig. 32.1 Adrenal steroid biosynthesis in SW-CAH. Abbreviations: P450c21 21-hydroxylase enzyme (CYP21A2), P450scc side chain cleavage enzyme catalyzing the rate limiting step in steroid biosynthesis (CYP11A1), P450c17 17α-hydroxylase/17,20 lyase (CYP17A1), 3βHSD2 3β-hydroxysteroid dehydrogenase type 2 (HSD3B2), P450c11β 11β-hydroxylase/cortisol synthase (CYP11B1), P450c11AS 11β-hydroxylase/aldosterone synthase (CYP11B2), 5αR2 5α-reductase 2, 11βHSD2 11β-hydroxysteroid dehydrogenase 2 (HSD11B2), 17βHSD5 17β-hydroxysteroid dehydrogenase (HSD17B)

Case Presentation

The now 18-year-old young man presented at the age of 1 week with failure to thrive, vomiting, hyponatremia (se Na 125 mmol/L, normal: 135–145), and hyperkalemia (se K 6.1 mmol/L, normal 3.5–5.5). He was born full term with birth weight 3250 g, but his weight decreased to 2750 g by 1 week. Upon physical examination a hyperpigmented and wrinkled scrotum was observed on the severely dehydrated and undernourished neonate. Intensive fluid and electrolyte therapy was immediately started and intravenous hydrocortisone substitution was introduced with stress dosing (50 mg bolus followed by 100 mg/m^2/day). Karyotype was 46,XY normal male. 17-Hydroxyprogesterone (17-OHP) was 10,350 ng/dL (normal for age 5–200 ng/dL). The genetic analysis of the *CYP21A2* gene revealed Q318X/Del com-

pound heterozygous mutations, corresponding to SW-CAH.

After initiation of combined glucocorticoid and mineralocorticoid substitution therapy, he improved quickly, started to gain weight and develop normally. He was hospitalized nearly every year for severe salt wasting associated with intercurrent infections. However, appropriate hormonal suppression was very difficult to achieve. The left adrenal was removed during infancy based on assumption of adrenal autonomous hormone production, however, this did not completely solve the difficulty in suppressing adrenal androgen production. Androgen excess caused accelerated growth velocity and central precocious pubarche (see later). He received GnRH depot (gonadotropin-releasing hormone) therapy to delay pubertal development between 5 and 12 years of age (Fig. 32.2).

At the age of 14, he started boarding school and developed serious compliance problems. Testicular adrenal rest tissue (TART) was first detected at the age of 16, and currently several 4–5 mm nodes are seen on both sides. Episodes of hypertension were detected by the school's

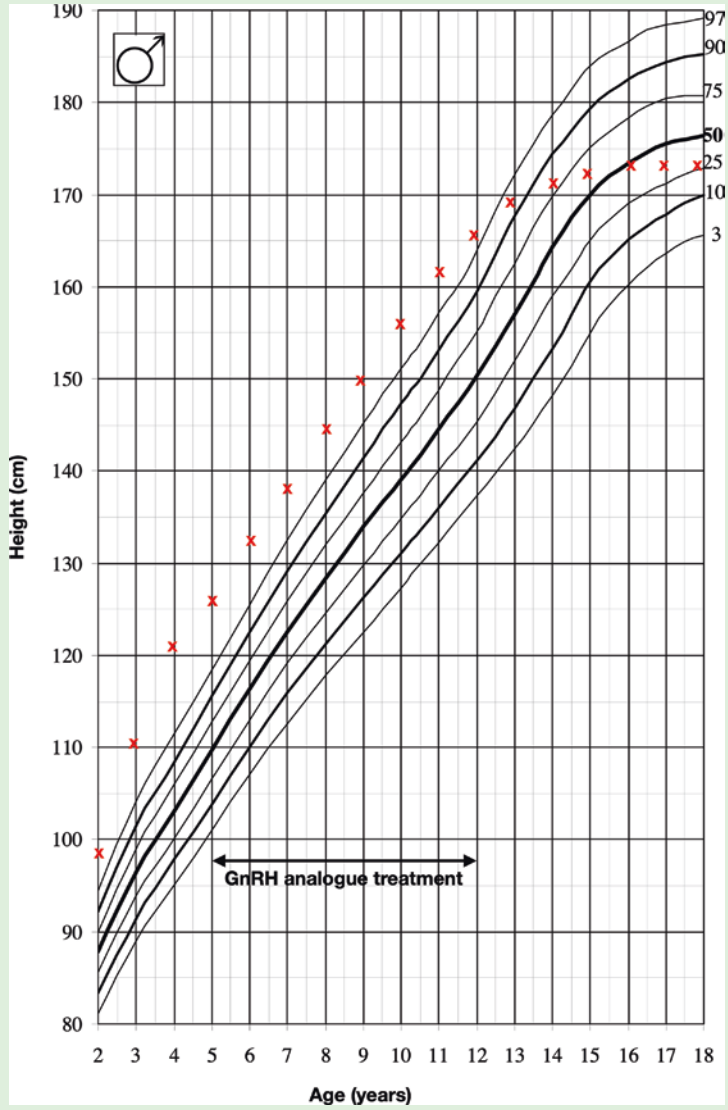

Fig. 32.2 Growth chart of the SW-CAH male patient

doctor. His current medication is hydrocortisone 15-15-0 mg (20.3 mg/m^2), fludrocortisone 0.05 mg BID and free sodium chloride consumption. He has reached a final height (173.5 cm, same as father), his weight is 83 kg, his skin is hyperpigmented, and he suffers from severe acne. Hormone panel at the last checkup is shown in Table 32.1.

He has one affected younger brother who was diagnosed right after birth before the development of salt wasting crisis and two unaffected sisters.

Table 32.1 Hormone results at the last checkup, incomplete suppression of adrenal excess androgen synthesis

		Normal range	
Na^+	137	134–146	mmol/L
K^+	4.3	4.0–5.0	mmol/L
Plasma renin activity	3.09	0.1–4.95	ng/mL/h
ACTH	145	5–60	pg/mL
Androstenedione	922	17–82	ng/dL
17-OHP	7587	40–250	ng/dL
Free testosterone	147.33	65–250	pg/mL
Total testosterone	4.67	3–8	ng/mL

How is SW-CAH diagnosed?

SW-CAH is part of most neonatal screening programs in developed countries. Most screening programs measure 17-OHP, the compound before the enzymatic block from dried blood spot samples by immunometry or mass chromatography. The positive screening result should be confirmed by other methods, for example, ACTH stimulation test (250 μg cosyntropin i.v., 17-OHP is measured at 0 and 60 min) or genetic diagnosis. However, at the time of birth of the above patient neonatal screening was not in effect in Hungary. SW-CAH girls are born with ambiguous genitalia which raises the suspicion of CAH and makes it possible to prevent the life-threatening salt wasting crisis, however, our patient was a boy and had to suffer early severe salt wasting. Without appropriate hormone substitution, patients rarely survive into childhood.

What are the diagnostic criteria for 21-OHD when using an ACTH stimulation test?

ACTH stimulation test is used to determine the cortisol secreting capacity of the adrenals. If cortisol secretion is blocked at the level of 21-hydroxylase, instead of cortisol 17-OHP, the intermediate compound is increased. 250 μg cosyntropin (tetracosactide) is administered i.v. and blood samples are taken at 0 and 60 min. A 17-OHP concentration above 1000 ng/dL in the 60 min sample is diagnostic for 21-OHD.

Is genetic diagnosis necessary?

Genetic diagnosis can provide useful information on the severity and type of the disease (i.e., SW- vs. SV-CAH which cannot be reliably differentiated by neonatal screening) with implications on the necessity of mineralocorticoid substitu-

tion therapy. Genetic diagnosis also provides important information on family planning. Prenatal diagnosis of CAH by chorion villous sampling is possible; however, prenatal therapy aiming suppression of intrauterine androgen excess remains experimental.

What is a salt wasting crisis?

Salt wasting crisis is a result of both mineralocorticoid and glucocorticoid deficiency. It occurs in untreated SW-CAH or if the patient cannot or did not take the appropriate medication (e.g., due to a gastrointestinal infection). Glucocorticoid deficiency causes hypoglycemia, low blood pressure, and unresponsiveness of blood vessels to stressors. Mineralocorticoid deficiency causes renal sodium loss and hyponatremia, hyperkalemia, hypovolemia, and low blood pressure. Hyponatremia causes increased intracranial pressure, seizures, and vomiting which further complicates electrolyte imbalance. Vomiting, low blood pressure, and weakness cause feeding inability in the newborn and weight loss. (The salt wasting crisis corresponds to the acute adrenal crisis in adults discussed in ► Chap. 31 on Addison's disease and autoimmune polyendocrine syndrome type 2.)

What is the differential diagnosis of a salt wasting crisis?

Neonatal sepsis can cause hyponatremia, failure to thrive, hypoglycemia, and seizures. In addition, in states of adrenal crisis, neonates are more prone to infections which might complicate the clinical picture. Renal insufficiency can cause similar electrolyte imbalances. Other causes of increased intracranial pressure can cause seizures and vomiting. In salt wasting crisis, hyponatremia leads to increased intracranial pressure. Other rare causes of congenital impaired mineralocorticoid synthesis (e.g., StAR deficiency and congenital adrenal hypoplasia) should also be considered.

How is SW-CAH treated?

SW-CAH patients need lifelong combined substitution therapy with mineralocorticoid and glucocorticoid. The goal of the therapy is to correct the cortisol and aldosterone deficiency and suppress excess adrenal androgen production. In children 10–15 mg/m^2/day hydrocortisone is given in three doses to minimize periods of overtreatment and risk of adrenal crisis. After closure of the growth plates, hydrocortisone can be switched to once daily steroid compounds, for example, dexamethasone or prednisone. Fludrocortisone 0.05–2.0 mg daily is recommended for mineralocorticoid substitution. Infants usually need sodium chloride tablets 1–2 g daily, later children develop the sense of salt craving and eat table salt by the spoonful in episodes of low sodium. Mineralocorticoid requirement can decrease over time.

In episodes of extreme biological stress (e.g., infections, fever, and surgical procedures) the substitution dose should be increased. Depending on the severity of the stress 50–100 mg/m^2/day hydrocortisone is recommended. In non-life-threatening stress, if the patient is able to take medication orally, maintenance dose should be increased to two to three times. The use of the hydrocortisone injection kit for emergency use is recommended (25 mg for infants, 50 mg under 40 kg, and 100 mg above 40 kg). Family members should also be familiar with use of the kit. It is recommended to carry some kind of MedicAlert accessory (card or bracelet) with basic details of steroid dependency.

Sometimes appropriate substitution is not possible to achieve or despite good substitution other related conditions need medical attention. Androgen excess in childhood leads to accelerated bone age and early epiphyseal closure leading to short final height. Final height can be improved by growth hormone therapy. If chronic androgen excess triggers central

precocious puberty, the pubertal process can be stopped by gonadotropin-releasing hormone (GnRH) analogue treatment, as it was needed in our patient. Women might have androgenic symptoms despite appropriate substitution, antiandrogenic therapy, for example, spironolactone might be needed. Women with PCOS-like symptoms might benefit from oral contraceptives.

Which forms of precocious puberty are known and how is precocious puberty defined?

The first signs of puberty appear normally between 8 and 13 years in girls and 9 and 14 years in boys. The normal pubertal development is preceded by an increase in adrenal steroid genesis from the age of 5–6 years. Usually it does not cause any visible clinical signs, but in some cases pubic hair growth (pubarche) or aromatic body odor occur. These are normal phenomena. However, signs of central, gonadotropin related puberty before the age of 8 years in girls and 9 years in boys is considered precocious puberty: breast development in girls, testicular enlargement in boys, pubic hair growth, accelerated longitudinal growth, gonadotropin elevation, and a prominent LH response in the GnRH stimulation test (luteinizng hormone (LH)/follicle stimulating hormone (FSH) greater than 1.5 after iv gonadotropin injection (2.5 μg/kg, maximum 100 μg) and blood is taken at 0, 30, and 60 minutes). On the other hand, early pubertal signs without gonadotropin involvement, due to peripheral autonomous hormone production (e.g., CAH, adrenal, ovarian, or testicular tumors) are called precocious pseudopuberty to differentiate from the gonadotropin-driven process. In precocious pseudopuberty, there is no spermato- or oogenesis, on the other hand in central precocious puberty, germ cells can be produced, and therefore children can turn fertile. High levels of androgens, however, as in our case can induce central, gonadotropin-dependent precocious puberty, as well.

What is TART?

Testicular adrenal rest tissue (TART) refers to islets of steroidogenic cells in the testicles which increase in size in response to the stimulatory effect of supraphysiological concentrations of ACTH. TART formation is usual in male CAH patients after puberty and it might lead to subfertility by compression of seminiferous tubules. Optimal substitution might decrease TART.

What are the possible complications of SW-CAH?

The most important complication of SW-CAH is adrenal crisis. However, both under- and overtreatment can lead to a number of chronic conditions. Cardiovascular morbidities, low or high blood pressure, metabolic syndrome, decreased bone mass, subfertility in both genders and mental health issues might emerge. See in detail in the next chapter on SV-CAH.

How is genital ambiguity treated in girls?

The optimal treatment of genital ambiguity is a matter of debate. Since fertility can be achieved by appropriate hormonal treatment, in 46,XX girls female gender of rearing is recommended. There is a debate over timing and technique of surgery (one stage or two stages). Early surgery might lead to decreased intercourse frequency, sexual difficulties, urinary leakage, and urinary infections. However, postponing surgery to later ages might raise psychosocial issues.

Tips

The reader is advised to read the chapter on Addison's disease and autoimmune polyendocrine syndrome type 2 (► Chap. 31) and the chapter on polycystic ovary syndrome (► Chap. 39).

Take Home Messages

- 21-Hydroxylase deficiency is responsible for 95% of all congenital adrenal hyperplasia (CAH) cases, and 75% of classical CAH cases is SW-CAH.
- 21-OHD is part of the neonatal screening programs and without screening boys who don't have ambiguous genitalia might be lost.
- If SW-CAH is not treated, it leads to life-threatening salt wasting crisis.
- Hormonally, SW-CAH is characterized by lack of cortisol and aldosterone and excess testosterone production, high ACTH and 17-OHP levels.
- SW-CAH is treated with combination of hydrocortisone, fludrocortisone, and sodium chloride.

Suggested Reading

1. Bonfig W. Growth and development in children with classic congenital adrenal hyperplasia. Curr Opin Endocrinol Diabetes Obes. 2017;24(1):39–42. https://doi.org/10.1097/MED.0000000000000308.
2. El-Maouche D, Arlt W, Merke DP. Congenital adrenal hyperplasia [published correction appears in Lancet. 2017 Nov 11;390(10108):2142]. Lancet. 2017;390(10108):2194–210. https://doi.org/10.1016/S0140-6736(17)31431-9.
3. Engels M, Span PN, van Herwaarden AE, Sweep FCGJ, Stikkelbroeck NMML, Claahsen-van der Grinten HL. Testicular adrenal rest tumors: current insights on prevalence, characteristics, origin, and treatment. Endocr Rev. 2019;40(4):973–87. https://doi.org/10.1210/er.2018-00258.
4. Jha S, El-Maouche D, Marko J, Mallappa A, Veeraraghavan P, Merke DP. Individualizing management of infertility in classic congenital adrenal hyperplasia and testicular adrenal rest tumors. J Endocr Soc. 2019;3(12):2290–4. https://doi.org/10.1210/js.2019-00227, Published 2019 Oct 17.
5. Khattab A, Marshall I. Management of congenital adrenal hyperplasia: beyond conventional glucocorticoid therapy. Curr Opin Pediatr. 2019;31(4):550–4. https://doi.org/10.1097/MOP.0000000000000780.
6. Maccabee-Ryaboy N, Thomas W, Kyllo J, Lteif A, Petryk A, Gonzalez-Bolanos MT, Hindmarsh PC, Sarafoglou K. Hypertension in children with congenital adrenal hyperplasia. Clin Endocrinol. 2016;85(4):528–34. https://doi.org/10.1111/cen.13086.
7. Morani AC, Jensen CT, Habra MA, Agrons MM, Menias CO, Wagner-Bartak NA, Shaaban AM, Roman-Colon AM, Elsayes KM. Adrenocortical hyperplasia: a review of clinical presentation and imaging. Abdom Radiol (NY). 2020;45(4):917–27. https://doi.org/10.1007/s00261-019-02048-6.
8. New M, Yau M, Lekarev O, Lin-Su K, Parsa A, Pina P, Yuen T, Khattab A. Congenital adrenal hyperplasia. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext. South Dartmouth: MDText.com, Inc.; 2000.
9. Ng SM, Stepien KM, Krishan A. Glucocorticoid replacement regimens for treating congenital adrenal hyperplasia. Cochrane Database Syst Rev. 2020;(3):CD012517. https://doi.org/10.1002/14651858.CD012517.pub2, Published 2020 Mar 19.
10. Parsa AA, New MI. Steroid 21-hydroxylase deficiency in congenital adrenal hyperplasia. J Steroid Biochem Mol Biol. 2017;165(Pt A):2–11. https://doi.org/10.1016/j.jsbmb.2016.06.015.
11. Speiser PW, Azziz R, Baskin LS, Baskin LS, Conway GS, Merke DP, Meyer-Bahlburg HFL, Miller WL, Murad MH, Oberfield SE, White PC. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline [published correction appears in J Clin Endocrinol Metab. 2010 Nov;95(11):5137]. J Clin Endocrinol Metab. 2010;95(9):4133–60. https://doi.org/10.1155/2010/494173.
12. van der Linde AAA, Schönbeck Y, van der Kamp HJ, van den Akker ELT, van Albada ME, Boelen A, Finken MJJ, Hannema SE, Hoorweg-Nijman G, Odink RJ, Schielen PCJI, Straetemans S, van Trotsenburg PS, Claahsen-van der Grinten HL, Verkerk PH. Evaluation of the Dutch neonatal screening for congenital adrenal hyperplasia. Arch Dis Child. 2019;104(7):653–7. https://doi.org/10.1136/archdischild-2018-315972.
13. Yau M, Khattab A, Poppas D, Ghizzoni L, New M. Congenital adrenal hyperplasia: unresolved issues. Front Horm Res. 2016;46:184–95. https://doi.org/10.1159/000443919.

Simple Virilizing 21-Hydroxylase Deficiency

Dóra Török and Judit Tőke

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_33

Opening

Congenital adrenal hyperplasia (CAH) is a group of inherited disorders of cortisol biosynthesis in the adrenal cortex. 21-Hydroxylase deficiency (21-OHD) is the most common form of CAH. 21-OHD is further divided into classical and non-classical forms. Nearly 25% of classical CAH patients have the simple virilizing type of CAH (SV-CAH). The incomplete loss of 21-hydroxylase activity allows it to produce enough aldosterone to avoid salt wasting, but not enough cortisol to maintain effective negative feedback on adrenocorticotropic hormone (ACTH) production. Alterations in adrenal hormone synthesis driven by excess ACTH results in early androgen excess causing virilization symptoms in females both in utero and later in life. SV-CAH patients need lifelong hormone replacement therapy and close monitoring for not only endocrine but also numerous other health related problems.

Definition of the Disease

The definition and pathophysiological background is discussed in detail in the previous chapter (► Chap. 32) on salt wasting congenital adrenal hyperplasia. Briefly, simple virilizing CAH belongs to the classical 21-hydroxylase deficiency subgroup of congenital adrenal hyperplasias. Nearly 25% of classical 21-OHD cases are SV-CAH. It is caused by mutation of the 21-hydroxylase enzyme allowing 1–2% of residual enzyme activity. This is enough to produce enough aldosterone to avoid a life-threatening salt wasting crisis but not enough to provide effective negative cortisol feedback on ACTH production. The excess ACTH has a trophic effect on the adrenal, causing adrenocortical hyperplasia and alterations of adrenal steroid synthesis including glucocorticoid precursors diverted to the androgen synthesis pathway. Excess androgen production starts already in early fetal life leading to virilization of the female fetus and formation of ambiguous genitalia. The effect of excess androgen on the male fetus is less visible. The enzymatic block leads to an increase in 17-Hydroxyprogesterone (17-OHP) (■ Fig. 33.1), however, this increase is less pronounced in SV-CAH than in SW-CAH, therefore neonatal screening is less effective in identifying SV-CAH patients.

If not treated, excess androgen production leads to progressive virilization and precocious pubarche (development of pubic hair) and adrenarche (increased adrenal androgen production) in infancy. Salt loss does not occur under normal conditions; however, in situations of extreme biological stress, for example, severe gastrointestinal infections, adrenal crisis, and salt loss might be provoked.

SV-CAH patients need lifelong glucocorticoid substitution treatment. In infancy, low doses of mineralocorticoid treatment might be beneficial. After puberty, androgen excess might be a problem despite appropriate substitution, and antiandrogen therapy might be beneficial. Even at the best glucocorticoid dosing, episodes of under- and overtreatment occur during the day which has several long-term metabolic consequences. Hypertension, metabolic syndrome, insulin resistance, osteopenia, and subfertility are important issues in both men and women.

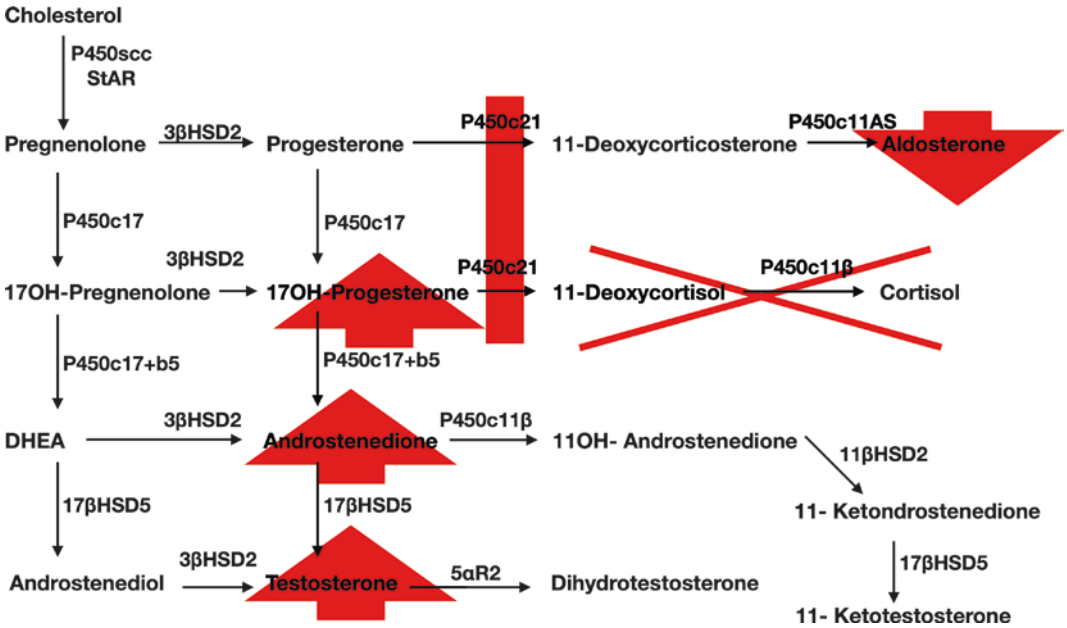

Fig. 33.1 Adrenal steroid biosynthesis in SV-CAH. Abbreviations: P450c21 21-hydroxylase enzyme (*CYP21A2*), P450scc side chain cleavage enzyme catalyzing the rate limiting step in steroid biosynthesis (*CYP11A1*), P450c17 17α-hydroxylase/17,20 lyase (*CYP17A1*), 3βHSD2 3β-hydroxysteroid dehydrogenase type 2 (*HSD3B2*), P450c11β 11β-hydroxylase/cortisol synthase (*CYP11B1*), P450c11AS 11β-hydroxylase/aldosterone synthase (*CYP11B2*), 5αR2 5α-reductase 2, 11βHSD2 11β-hydroxysteroid dehydrogenase 2 (*HSD11B2*), 17βHSD5 17β-hydroxysteroid dehydrogenase (*HSD17B*)

Case Presentation

The 43-year-old woman was diagnosed at the age of 2 years based on virilized genitalia, clitoromegaly without posterior labial fusion, precocious pubarche, early pubic hair growth, and intensive longitudinal growth. 17-Hydroxyprogesterone was 3471 ng/ml (1–200 ng/ml). Electrolytes were normal, salt wasting was not observed. Substitution therapy was initiated with hydrocortisone (5 mg tid) and genital reconstruction surgery (clitoroplasty) was done after diagnosis. She suffered several febrile illnesses during childhood, appropriate increasing of the usual hydrocortisone substitution was enough to prevent the need for hospital admission. Menarche (first menstrual bleeding) occurred at the age of 16 years; period has always been irregular. She is married. Genetic diagnosis was made in young adulthood, the observed genotype was I172N/I172N corresponding to the SV-CAH phenotype. Pregnancy was achieved by assisted reproduction techniques, ovulation induction, and insemination. Currently she is treated with a combination of hydrocortisone and dexamethasone (hydrocortisone 10-7.5-5 mg daily, dexamethasone 0.25 mg daily in the evening). She also receives medical treatment for hypercholesterolemia and hypertension. She has osteopenia. Latest hormonal checkup is summarized in Table 33.1.

She has a younger sister with the same genetic background and similar clinical presentation.

Table 33.1 Hormone results at the last checkup

		Normal range	
Na^+	137	134–146	mmol/L
K^+	4.6	4.0–5.0	mmol/L
Plasma renin activity	2.7	0.1–4.95	ng/mL/h
ACTH	241	5–60	pg/mL
Androstenedione	294.2	80–280	ng/dL
17-OHP	9287	3–150	ng/dL

How is SV-CAH diagnosed?

The diagnosis of SV-CAH is the same as for SW-CAH and is presented in detail in the preceding chapter. The neonatal screening is less effective in identifying SV-CAH cases than SW-CAH. SV-CAH and SW-CAH cannot be differentiated if identified by newborn screening before the symptoms of salt wasting occur; therefore all identified neonates are started on combination of glucocorticoid and mineralocorticoid substitution. Later, based on genetic diagnosis and hormonal follow-up, careful cessation of mineralocorticoid substitution might be attempted if SV-CAH is suspected.

In our case genetic diagnosis was made at a later age, and the genetic background of 21-OHD was unknown when she was born. However, it provided important information on genetic counseling during her family planning. It was reassuring that her husband did not carry any mutations in the *CYP21A2* gene; therefore their baby was not at risk of developing CAH.

What causes ambiguous genitalia in CAH?

Impaired cortisol production does not provide an effective negative feedback loop on pituitary ACTH production. The excess ACTH causes adrenocortical hyperplasia and excess androgen production, mostly androstenedione and testosterone. This starts as early as eighth week of gestation. Excess fetal androgens cause virilization of the external genitalia of the female fetus while Müllerian derived organs, uterus, Fallopian tubes, and ovaries are intact. The extent of virilization of external genitalia is variable and depends on the severity of disease. It ranges from mild clitoromegaly to complete posterior labial fusion with severe clitoromegaly, mimicking cryptorchidism with or without hypospadias. The latter case might lead to erroneous gender assignment which has a serious impact on the quality of life of these patients if not recognized and corrected early enough.

What is the differential diagnosis of ambiguous genitalia?

SV-CAH girls with ambiguous genitalia should be differentiated from other types of disorders of sex development (DSD). Karyotyping differentiates from undervirilized 46,XY male DSD. Further differential diagnosis includes other types of CAH (e.g., 11-beta-hydroxylase deficiency, characterized by hypertension and elevated deoxycorticosterone concentrations), androgen-producing ovarian or adrenal tumors, teratogenic maternal androgen excess (e.g., maternal anti-estrogen treatment during pregnancy for hormone sensitive breast tumor).

What causes precocious pubarche in SV-CAH?

If SV-CAH is not recognized and treated from early on (lack of neonatal screening, boys without visible virilization, or patients who miss neonatal screening) continuous androgen excess causes signs of early pubarche and adrenarche in both boys and girls. This process is gonadotropin independent and driven solely by adrenal androgen production. Longitudinal growth is accelerated, pubic hair and axillary growth and aromatic body odor are characteristic. Penis length is increased in boys and the scrotum is pigmented and wrinkled; however, testicular size is prepubertal because of low gonadotropins. Breast development and menarche in girls do not occur.

However, longstanding androgen excess might lead to central, gonadotropin driven precocious pubarche in rare cases.

What is the differential diagnosis of precocious pubarche and adrenarche?

Adrenarche after the age of 5–6 years might be a normal phenomenon, if not progressive and 17-OHP is not increased. Precocious pubarche should be differentiated from central, gonadotropin driven precocious pubarche based on physical examination (see above) and gonadotropin releasing hormone (GnRH) stimulation test. Androgen-producing testicular, ovarian, and adrenal tumors should be ruled out. Brain tumor, previous injury, hypoxia, or inherited diseases (e.g., neurofibromatosis) might prompt central precocious puberty. Gigantism due to growth hormone overproduction causes accelerated longitudinal growth but not sexual maturation.

How is SV-CAH treated?

SV-CAH patients need lifelong substitution glucocorticoid therapy. If the diagnosis was made early by means of newborn screening therapy is usually started with the assumption of the most serious, salt wasting disease with a combination of mineralocorticoids and glucocorticoids. Later, if diagnosis of SV-CAH is confirmed by genetic diagnosis and careful clinical and hormonal follow-up, mineralocorticoid treatment can be stopped. However, some patients achieve better hormonal control if a small amount of mineralocorticoid is also administered.

The goal of the therapy is to correct the cortisol deficiency and suppress excess adrenal androgen production. In children 10–15 mg/m^2/day hydrocortisone is given in three doses to minimize periods of overtreatment and risk of adrenal crisis. After closure of the growth plates hydrocortisone can be switched to once daily steroid compounds, for example, dexamethasone or prednisone. Some patients achieve a better control with a combination of hydrocortisone and dexamethasone treatment, like in our case.

In episodes of extreme biological stress (e.g., infections, fever, and surgical procedures) the substitution dose should be increased similarly to SW-CAH patients. It is recommended to carry some kind of Medic-Alert accessory (card or bracelet) with basic details of steroid dependency.

What are the possible complications of SV-CAH?

Although SV-CAH patients are not at particular risk for salt wasting, adrenal crisis under extreme biological stress might occur. In adult SV-CAH patients several chronic health conditions might be of concern. Cardiovascular morbidity and mortality are increased in CAH. The major cardiovascular risk factor is obesity and overweight, this is already a major problem in childhood. Overall and abdominal body fat is increased in CAH patients compared to the normal population. The frequency of metabolic syndrome is also increased in CAH. Hypertension becomes a concern in later ages. Insulin resistance and high blood glucose levels are linked to both overweight and glucocorticoid overtreatment. Interestingly, undertreatment with glucocor-

ticoids induces impaired insulin sensitivity as well. The incidence of diabetes is increased in CAH. There is also an increased risk of combined hyperlipidemia, venous thromboembolism, and atrial fibrillation.

- Bone health is impaired in both adult men and women with CAH. The increased fracture risk and low bone mineral density is linked to glucocorticoid excess. Hypogonadotropic hypogonadism, especially in males caused by the negative feedback of adrenal androgen excess on the hypothalamus, might also have adverse effects on bone mass. On the other hand, excess androgens are converted to estrogen which has protective effects on the bone. Males are more affected by osteopenia and osteoporosis than women.

- Both males and females suffer from increased risk of various psychiatric problems.

- The number of pregnancies is reduced in female CAH patients; however, pregnancies themselves are usually healthy. There are several factors behind the reduced fertility: reduced heterosexual partnership, effects of genital surgery, anovulation, and progesterone hypersecretion. Fertility rate is the lowest in the most severely affected SW-CAH population.

- Fertility rate in male CAH patients is also decreased. Adrenal androgen excess causes gonadotropin suppression and hypogonadotropic hypogonadism. ACTH overproduction causes testicular adrenal rest tissue (TART) formation (see the chapter on SW-CAH) which compresses seminiferous tubules and causes testicular failure. TART formation can be treated by excessive amounts of glucocorticoids which have serious side effects. On the other hand, glucocorticoid overdosing leads to secondary hypogonadotropic hypogonadism.

- Chronic ACTH stimulation causes adrenocortical overgrowth. Adrenal volumes correlate well with disease markers (ACTH and androstenedione), and sometimes large adrenocortical tumors can form. Myelolipomas can grow large and sometimes have to be removed because of mass effects; however, malignant adrenal tumors are rare.

Tips

The reader is advised to read the next chapter on late onset 21-hydroxylase deficiency (▶ Chap. 34). A rare form of CAH is discussed in the chapter on 17α hydroxylase/17,20 lyase deficiency (▶ Chap. 35), where other CAH forms are also briefly discussed. Moreover, the reader is advised to read the chapter on Addison's disease and autoimmune polyendocrine syndrome type 2 (▶ Chap. 31) and the chapter on polycystic ovary syndrome (▶ Chap. 39).

Take Home Messages

- 21-Hydroxylase deficiency is responsible for 95% of all CAH cases; 25% of classical CAH cases is SV-CAH.
- 21-OHD is part of the neonatal screening programs, but SV-CAH patients are not always found by the screening.
- Hormonally SV-CAH is characterized by lack of cortisol and excess testosterone production, high ACTH and 17-OHP levels, but not mineralocorticoid deficiency.
- SV-CAH is treated with glucocorticoids and sometimes antiandrogens.

Suggested Reading

1. Almasri J, Zaiem F, Rodriguez-Gutierrez R, Tamhane SU, Iqbal AM, Prokop LJ, Speiser PW, Baskin LS, Bancos I, Murad MH. Genital reconstructive surgery in females with congenital adrenal hyperplasia: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2018;103(11):4089–96. https://doi.org/10.1210/jc.2018-01863.

2. Auchus RJ, Witchel SF, Leight KR, Aisenberg J, Azziz R, Bachega TA, Baker LA, Baratz AB, Baskin LS, Berenbaum SA, Breault DT, Cerame BI, Conway GS, Eugster EA, Fracassa S, Gearhart JP, Geffner ME, Harris KB, Hurwitz RS, Katz AL, Kalro BN, Lee PA, Alger Lin G, Loechner KJ, Marshall I, Merke DP, Migeon CJ, Miller WL, Nenadovich TL, Oberfield SE, Pass KA, Poppas DP, Lloyd-Puryear MA, Quigley CA, Riepe FG, Rink RC, Rivkees SA, Sandberg DE, Schaeffer TL, Schlussel RN, Schneck FX, Seely EW, Snyder D, Speiser PW, Therrell BL, Vanryzin C, Vogiatzi MG, Wajnrajch MP, White PC, Zuckerman AE. Guidelines for the development of comprehensive care centers for congenital adrenal hyperplasia: guidance from the CARES Foundation initiative. Int J Pediatr Endocrinol. 2010;2010:275213. https://doi.org/10.1155/2010/275213.
3. Bachelot A. Transition of care from childhood to adulthood: congenital adrenal hyperplasia. Endocr Dev. 2018;33:17–33. https://doi.org/10.1159/000487523.
4. Gomes LG, Bachega TASS, Mendonca BB. Classic congenital adrenal hyperplasia and its impact on reproduction. Fertil Steril. 2019;111(1):7–12. https://doi.org/10.1016/j.fertnstert.2018.11.037.
5. Gomes LG, Mendonca BB, Bachega TASS. Long-term cardio-metabolic outcomes in patients with classical congenital adrenal hyperplasia: is the risk real? Curr Opin Endocrinol Diabetes Obes. 2020;27(3):155–61. https://doi.org/10.1097/MED.0000000000000545.
6. Jesus LE. Feminizing genitoplasties: where are we now? J Pediatr Urol. 2018;14(5):407–15. https://doi.org/10.1016/j.jpurol.2018.03.020.
7. Reisch N. Review of health problems in adult patients with classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Exp Clin Endocrinol Diabetes. 2019;127(2–03):171–7. https://doi.org/10.1055/a-0820-2085.
8. Rapp M, Mueller-Godeffroy E, Lee P, Roehle R, Kreukels BPC, Köhler B, Nordenström A, Bouvattier C, Thyen U. Multicentre cross-sectional clinical evaluation study about quality of life in adults with disorders/differences of sex development (DSD) compared to country specific reference populations (DSD-LIFE). Health Qual Life Outcomes. 2018;16(1):54. https://doi.org/10.1186/s12955-018-0881-3.
9. Bonfig W. Growth and development in children with classic congenital adrenal hyperplasia. Curr Opin Endocrinol Diabetes Obes. 2017;24(1):39–42. https://doi.org/10.1097/MED.0000000000000308.
10. El-Maouche D, Arlt W, Merke DP. Congenital adrenal hyperplasia [published correction appears in Lancet. 2017 Nov 11;390(10108):2142]. Lancet. 2017;390(10108):2194–210. https://doi.org/10.1016/S0140-6736(17)31431-9.
11. Engels M, Span PN, van Herwaarden AE, Sweep FCGJ, Stikkelbroeck NMML, Claahsen-van der Grinten HL. Testicular adrenal rest tumors: current insights on prevalence, characteristics, origin, and treatment. Endocr Rev. 2019;40(4):973–87. https://doi.org/10.1210/er.2018-00258.
12. Jha S, El-Maouche D, Marko J, Mallappa A, Veeraraghavan P, Merke DP. Individualizing management of infertility in classic congenital adrenal hyperplasia and testicular adrenal rest tumors. J Endocr Soc. 2019;3(12):2290–4. https://doi.org/10.1210/js.2019-00227, Published 2019 Oct 17.
13. Khattab A, Marshall I. Management of congenital adrenal hyperplasia: beyond conventional glucocorticoid therapy. Curr Opin Pediatr. 2019;31(4):550–4. https://doi.org/10.1097/MOP.0000000000000780.
14. Maccabee-Ryaboy N, Thomas W, Kyllo J, Lteif A, Petryk A, Gonzalez-Bolanos MT, Hindmarsh PC, Sarafoglou K. Hypertension in children with congenital adrenal hyperplasia. Clin Endocrinol. 2016;85(4):528–34. https://doi.org/10.1111/cen.13086.
15. Morani AC, Jensen CT, Habra MA, Agrons MM, Menias CO, Wagner-Bartak NA, Shaaban AM, Roman-Colon AM, Elsayes KM. Adrenocortical hyperplasia: a review of clinical presentation and imaging. Abdom Radiol (NY). 2020;45(4):917–27. https://doi.org/10.1007/s00261-019-02048-6.
16. New M, Yau M, Lekarev O, Lin-Su K, Parsa A, Pina P, Yuen T, Khattab A. Congenital adrenal hyperplasia. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext. South Dartmouth: MDText.com, Inc.; 2000.
17. Ng SM, Stepien KM, Krishan A. Glucocorticoid replacement regimens for treating congenital adrenal hyperplasia. Cochrane Database Syst Rev. 2020;(3):CD012517. https://doi.org/10.1002/14651858.CD012517.pub2, Published 2020 Mar 19.
18. Parsa AA, New MI. Steroid 21-hydroxylase deficiency in congenital adrenal hyperplasia. J Steroid Biochem Mol Biol. 2017;165.(Pt A:2–11. https://doi.org/10.1016/j.jsbmb.2016.06.015.
19. Speiser PW, Azziz R, Baskin LS, Baskin LS, Conway GS, Merke DP, Meyer-Bahlburg HFL, Miller WL, Murad MH, Oberfield SE, White PC. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline [published correction appears in J Clin Endocrinol Metab. 2010 Nov;95(11):5137]. J Clin Endocrinol Metab. 2010;95(9):4133–60. https://doi.org/10.1155/2010/494173.
20. van der Linde AAA, Schönbeck Y, van der Kamp HJ, van den Akker ELT, van Albada ME, Boelen A, Finken MJJ, Hannema SE, Hoorweg-Nijman G, Odink RJ, Schielen PCJI, Straetemans S, van Trotsenburg PS, Claahsen-van der Grinten HL, Verkerk PH. Evaluation of the Dutch neonatal screening for congenital adrenal hyperplasia. Arch Dis Child. 2019;104(7):653–7. https://doi.org/10.1136/archdischild-2018-315972.
21. Yau M, Khattab A, Poppas D, Ghizzoni L, New M. Congenital adrenal hyperplasia: unresolved issues. Front Horm Res. 2016;46:184–95. https://doi.org/10.1159/000443919.

Late-Onset 21-Hydroxylase Deficiency

Peter Igaz

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_34

Opening

The two preceding chapters discussed the classical forms of 21-hydroxylase deficiency, that is, the salt wasting and simple virilizing forms. Late-onset, non-classical 21-hydroxylase deficiency is much more common than these, and it is usually diagnosed in young women with symptoms of androgen excess.

Definition of the Disease

The prevalence of late-onset, non-classic 21-hydroxylase deficiency varies between 1:100 and 1:1000 in different ethnic groups. In adult women and adolescent girls, androgen excess could result in oligomenorrhoea (in about 50% of affected cases), hirsutism (60%) and acne (in about 30% of cases). In children, the isolated development of sexual hair in boys and girls younger than 9 and 8 years, respectively (premature pubarche), advanced bone age and acne may be observed. Mutations in the *CYP21A2* gene coding for 21-hydroxylase can be identified.

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Case Presentation

The 30-year-old woman was referred to our consultation for secondary amenorrhea. She had her first menstrual cycle at the age of 13, but after a few spontaneous cycles, menstrual cycles could only be provoked by drug treatment. Based on hyperandrogenic signs (hirsutism and acne), the diagnosis of polycystic ovarian syndrome was established, and an oral contraceptive treatment was initiated. She was on oral contraceptive (OC) (ethinyl estradiol + cyproterone acetate) treatment for the past 10 years. (Cyproterone is a progesterone derivative with antiandrogenic action.)

What to Do First?

As the patient was on oral contraceptive (OC) treatment, the OC should be discontinued first for 3 months before blood for hormonal measurements can be taken. Hormonal results cannot be interpreted in patients on OC (except for, e.g. thyroid stimulating hormone (TSH) and free thyroxine (fT4)), as the oestrogen component influences many other hormone levels in part via the altered production of carrier proteins.

Table 34.1 summarizes the results of the first hormone panel after stopping OC 3 months earlier.

What can be inferred from this hormone panel (Table 34.1)?

The 17-OH-progesterone (17-hydroxyprogesterone) level is very high, whereas two androgens, that is, androstenedione and testosterone, are also elevated. As the basal 17-OH-progesterone exceeds 1000 ng/dL, there was no need for short adrenocorticotropic hormone (ACTH) (tetracosactide) stimulation test (Cosyntropin, Synacthen™) to confirm 21-hydroxylase deficiency. (Later, however, the ACTH test was performed, and the 60-min 17-OH-progesterone level after 250 µg tetracosactide was 3907 ng/dL, whereas the cortisol value was normal 23.4 µg/dL [normal >20 µg/dL].)

The suspicion for late-onset 21-hydroxylase deficiency can be raised if the basal 17-OH-progesterone is between 200 and 1000 ng/dL, but an ACTH stimulation test is needed to confirm the disease (the diagnostic cut-off for 17-OH-progesterone at 60 min after tetracosactide is >1000 ng/dL [by some authors >1500 ng/dL]).

Oral glucose tolerance test showed a normal response along with HOMA-index

Table 34.1 Results of the first hormonal screen taken in the morning

Hormone	Result	Normal range
TSH	0.92 mIU/L	0.35–4.94 mIU/L
Prolactin	6.07 ng/mL	1.39–24.20 ng/mL
Cortisol	23.7 µg/dL	8.0–25.0 µg/dL
Adrenocorticotropic hormone (ACTH)	56.0 pg/mL	7.2–63.3 pg/mL
Androstenedione	**551.0 ng/dL**	**80–280 ng/dL**
17-OH-progesterone	**2158.0 ng/dL**	**40.0–250.0 ng/dL**
Dehydroepiandrosterone sulfate (DHEAS)	323.0 µg/dL	130.0–330.0 µg/dL
Total testosterone	**75.0 ng/dL**	**20.0–60.0 ng/dL**
Cortisol after 1 mg overnight dexamethasone test	0.9 µg/dL	<1.8 µg/dL
Luteinizing hormone (LH)	8.4 IU/L	2.4–12.6 Follicular phase 14.0–95.6 Ovulatory phase 1.0–11.4 Luteal phase 7.7–58.5 Menopause
Follicle stimulating hormone (FSH)	4.6 IU/L	3.5–12.5 Follicular phase 4.7–21.5 Ovulatory phase 1.7–7.7 Luteal phase 25.8–134.8 Menopause
Estradiol (E2)	38.1 pg/mL	24.5–196 Follicular phase 66.1–411 Ovulatory phase 40.0–261 Luteal phase <10–39.2 Menopause

(homeostasis model assessment of insulin resistance). The previous diagnosis of polycystic ovarian syndrome could thus be revised, and the patient appeared to have late-onset 21-hydroxylase deficiency.

How should the disease be further confirmed?

Genetic testing should be performed. A homozygous V281L (Val281Leu) mutation was confirmed in the *CYP21A2* gene, that is, a typical mutation in late-onset non-classic 21-hydroxylase deficiency.

How should the patient be treated?

If there is no wish for pregnancy, oral contraceptive treatment is sufficient in these patients. Late-onset 21-hydroxylase-deficient patients usually do not have adrenal insufficiency (hypoadrenalism), and no steroid substitution is needed even in stress situations (see ▶ Chap. 31 on Addison's disease). This is shown by the result of the tetracosactide test, as well, where the stimulated cortisol was normal.

However, as our patient planned for pregnancy, steroid substitution was started first in a dose of daily 20 mg hydrocortisone. As the menstrual cycle has not restarted with hydrocortisone only, dexamethasone was also added (15 mg hydrocortisone + 0.125 mg dexamethasone in the evening).

How should treatment be monitored?

In patients treated with glucocorticoids, androstenedione, testosterone and 17-OH-

progesterone should be monitored. Androstenedione and testosterone should be normalized. There is no need to normalize 17-OH-progesterone, and fertility might be restored even with elevated 17-OH-progesterone. If the 17-OH-progesterone level is too low, it can be a marker of too high steroid doses used. Too high glucocorticoid doses could lead to iatrogenic hypercortisolism (increase in weight, obesity, decrease in bone mineral density, impaired glucose homeostasis, etc.). Therefore, the lowest effective dose should be given. (As discussed above, in patients taking OC, no hormonal monitoring can take place.)

Follow-up of the patient's case

Two months after the initiation of dexamethasone, a spontaneous menstrual cycle occurred (the first after more than 10 years). Four months later, she became pregnant (even when her 17-OH-progesterone was twice as high as the upper normal value). As dexamethasone crosses the placenta, and it is not inactivated by placental 11β-hydroxysteroid dehydrogenase type 2 (HSD11B2), it is not proposed during pregnancy. We therefore returned to hydrocortisone only. She gave birth to a healthy girl.

Is there a risk for 21-hydroxylase deficiency in the newborn?

21-hydroxylase deficiency is inherited as an autosomal recessive trait. However, as the mutations in the *CYP21A2* gene are relatively common, it can occur that the father of the child is a healthy heterozygous carrier. The prevalence of heterozygous carriers was estimated at 1:55, but in certain populations, even higher prevalence (even 1:10) can be observed. The risk for classic 21-hydroxylase deficiency in the offspring was estimated to be about 2.5% in women having the late-onset form (whereas about 15% of the offspring can be affected by the non-classic late-onset 21-hydroxylase deficiency). Genetic screening of the partner should be performed to assess the risk, but he was negative for the tested mutations.

Case presentation conclusion: Treatment outcome

The patient had two further successful pregnancies, and she is now mother of three healthy girls. As there is no further wish for fertility, we have returned to OC treatment.

Is treatment needed in men diagnosed with late-onset 21-hydroxylase deficiency?

Male patients are usually not diagnosed with late-onset 21-hydroxylase deficiency, as they are mostly devoid of any symptoms. Even if diagnosed (e.g. by genetic screening in a family), treatment is usually not needed. The only indication for treatment could be oligospermia. Testicular adrenal rest tissue (TART, discussed in more detail in the chapter on Salt wasting 21-hydroxylase deficiency) is uncommon in this form of disease.

Tips

- The reader is advised to read the two previous chapters on congenital adrenal hyperplasia (CAH; 21-hydroxylase deficiency: salt wasting and simple virilizing) before reading this chapter. Polycystic ovarian syndrome as the major differential diagnostic problem in the management of late-onset CAH is discussed in ▶ Chap. 39. The symptoms of Cushing's syndrome corresponding also to iatrogenic Cushing's syndrome (due to overtreatment) are discussed in ▶ Chap. 27 on adrenal Cushing's syndrome.

Take Home Messages

- Late-onset, non-classic 21-hydroxylase deficiency is more common than the classical, more severe forms (salt wasting and simple virilizing).
- The presented case was first considered to be a polycystic ovarian syndrome and treated with oral contraceptives, whereas it was actually a late-onset 21-hydroxylase deficiency.
- High 17-OH-progesterone confirmed diagnosis.
- Glucocorticoid treatment restored fertility.
- Late-onset 21-hydroxylase deficiency should be investigated in women suffering from oligomenorrhoea, hirsutism and infertility.

Suggested Reading

1. Baumgartner-Parzer SM, Nowotny P, Heinze G, Waldhäusl W, Vierhapper H. Carrier frequency of congenital adrenal hyperplasia (21-hydroxylase deficiency) in a middle European population. J Clin Endocrinol Metab. 2005;90(2):775–8. https://doi.org/10.1210/jc.2004-1728.
2. Carmina E, Dewailly D, Escobar-Morreale HF, Kelestimur F, Moran C, Oberfield S, Witchel SF, Azziz R. Non-classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency revisited: an update with a special focus on adolescent and adult women. Hum Reprod Update. 2017;23(5):580–99. https://doi.org/10.1093/humupd/dmx014.
3. El-Maouche D, Arlt W, Merke DP. Congenital adrenal hyperplasia. Lancet. 2017;390(10108):2194–210. https://doi.org/10.1016/s0140-6736(17)31431-9.
4. Falhammar H, Nordenstrom A. Nonclassic congenital adrenal hyperplasia due to 21-hydroxylase deficiency: clinical presentation, diagnosis, treatment, and outcome. Endocrine. 2015;50(1):32–50. https://doi.org/10.1007/s12020-015-0656-0.
5. Moran C, Azziz R, Weintrob N, Witchel SF, Rohmer V, Dewailly D, Marcondes JA, Pugeat M, Speiser PW, Pignatelli D, Mendonca BB, Bachega TA, Escobar-Morreale HF, Carmina E, Fruzzetti F, Kelestimur F. Reproductive outcome of women with 21-hydroxylase-deficient nonclassic adrenal hyperplasia. J Clin Endocrinol Metab. 2006;91(9):3451–6. https://doi.org/10.1210/jc.2006-0062.
6. Nordenstrom A, Falhammar H. Management of endocrine disease: diagnosis and management of the patient with non-classic CAH due to 21-hydroxylase deficiency. Eur J Endocrinol. 2019;180(3):R127–45. https://doi.org/10.1530/eje-18-0712.
7. Pang SY, Wallace MA, Hofman L, Thuline HC, Dorche C, Lyon IC, Dobbins RH, Kling S, Fujieda K, Suwa S. Worldwide experience in newborn screening for classical congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Pediatrics. 1988;81(6):866–74.
8. Papadakis G, Kandaraki EA, Tseniklidi E, Papalou O, Diamanti-Kandarakis E. Polycystic ovary syndrome and NC-CAH: distinct characteristics and common findings. A systematic review. Front Endocrinol. 2019;10:388. https://doi.org/10.3389/fendo.2019.00388.
9. Reisch N. Pregnancy in congenital adrenal hyperplasia. Endocrinol Metab Clin N Am. 2019;48(3):619–41. https://doi.org/10.1016/j.ecl.2019.05.011.
10. Speiser PW, White PC. Congenital adrenal hyperplasia. New Engl J Med. 2003;349:776–88. https://doi.org/10.1056/NEJMra021561.

17α-Hydroxylase/17, 20-Lyase Deficiency

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Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_35

Opening

17α-Hydroxylase/17,20-lyase deficiency is a rare form of congenital adrenal hyperplasia (CAH). In contrast to 21-hydroxylase deficiency that results in salt wasting and/or hyperandrogenic symptoms in women, 17α-hydroxylase/17,20-lyase deficiency leads to severe hypertension and hypokalaemia; moreover, alterations of sexual differentiation can also develop.

Definition of the Disease

As discussed in the previous chapters on 21-hydroxylase deficiency representing the most common form (about 95% of all cases), congenital adrenal hyperplasia (CAH) refers to the group of diseases where deficiencies of the steroid biosynthetic enzymes in the adrenal cortex lead to both hormone deficiencies and overproduction. Most forms of CAH result in the lack of cortisol that is sensed by the intact anterior pituitary and due to the feed-back regulation it answers by increasing adrenocorticotropic hormone (ACTH) production. ACTH, in turn, stimulates steroidogenesis, and thus, steroid precursors preceding the enzymatic block and steroid hormones of other pathways are overproduced. Due to the trophic effects of ACTH on the adrenal cortex, bilateral adrenal hyperplasia can be observed. In 21-hydroxylase deficiency, lack of cortisol (and in severe cases also aldosterone) is accompanied by an increased release of androgen precursors leading to adrenal insufficiency together with hyperandrogenism or infertility. Here we discuss 17α-hydroxylase/17,20-lyase deficiency, where the deficiency of this enzyme results in both cortisol and aldosterone deficiency; however, the precursors of aldosterone biosynthesis, 11-deoxycorticosterone (DOC) and corticosterone, are overproduced, resulting in severe hypertension and hypokalaemia. Due to the involvement of the 17α-hydroxylase/17,20-lyase enzyme (CYP17A1) in sex steroid biosynthesis, deficiency of both androgens and oestrogens can be observed leading to disorders of sexual differentiation and gonadal functioning (◘ Fig. 35.1). Another rare form of CAH is caused by 11β-hydroxylase deficiency, which is also related to mineralocorticoid excess due to DOC and corticosterone overproduction and thus hypertension and hypokalaemia, but similar to 21-hydroxylase deficiency, hyperandrogenism is observed (◘ Fig. 35.2). Deficiency of 3β-hydroxysteroid dehydrogenase 2 (HSD3B2), on the other hand, leads to lack of cortisol and aldosterone (hypotension and hyperkalaemia), whereas among sex steroids only dehydroepiandrosterone sulphate (DHEAS) is produced leading to ambiguous sexual differentiation (undervirilization of males and virilization of females) (◘ Fig. 35.3).

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Case Presentation

A 27-year-old woman was referred to our centre because of hypertension (blood pressure max: 180/100 mmHg) and hypokalaemia (se K+: 2.8–3.2 mmol/L, normal: 3.5–5.0). Her history includes operation of an ovarian cyst because of torquation at the age of 13. Her first menstrual cycle was at the age of 13, and then it came very rarely (once or twice per year). She took an oral contraceptive for the restoration of her menses since the age of 16 for 10 years, and since its omission 1 year earlier, she did not have any menstrual cycles. Phenotypically she was a normal female with normal breast development and secondary sexual characteristics. Her height was normal. She took only a Ca-antagonist against hypertension.

Which hormones should be determined in the first place?

Regarding hypertension and hypokalaemia, renin and aldosterone should be determined, and as a basic hormonal evaluation,

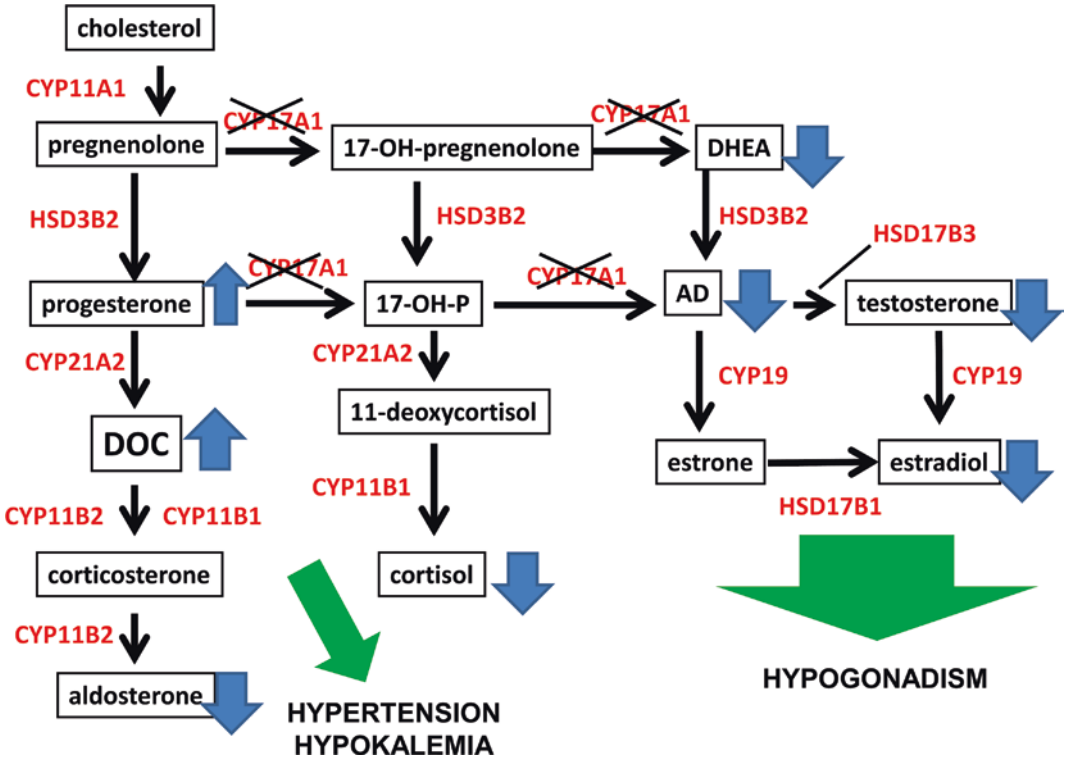

Fig. 35.1 Pathogenesis of 17α-hydroxylase/17,20-lyase (CYP17A1) deficiency. Lack of CYP17A1 results in decreased cortisol and sex steroid production, including both oestrogen and androgens (simplified overview of steroid hormone production). DOC production is, on the other hand, increased, leading to mineralocorticoid excess and subsequent hypertension with hypokalaemia. Aldosterone, on the other hand, is usually low. CYP11A1 cholesterol side chain cleavage enzyme (catalysing the rate-limiting enzymatic step in steroid biosynthesis), CYP11B1 cortisol synthase, CYP11B2 aldosterone synthase, CYP19 aromatase, CYP21A2 21-hydroxylase, HSD17B 17β-hydroxylase, 17-OHP 17-hydroxy-progesterone, AD androstenedione

cortisol, ACTH should also be determined. Regarding the secondary amenorrhoea, LH (luteinizing hormone), FSH (follicle stimulating hormone) and oestradiol (E2) should also be investigated.

✓ Table 35.1 summarizes the results of the first hormone panel.

? **What can be observed from this hormone panel (Table 35.1)?**

✓ Both cortisol and aldosterone are very low. ACTH is high underlining an adrenal cause of cortisol deficiency, whereas renin is suppressed. A 250 μg tetracosactide (ACTH analogue, cosyntropin containing the first 24 amino acids of ACTH but having full biological activity, see Diagnosis of Addison's disease and hypopituitarism (► Chaps. 6 and 31)) test was also performed, which showed no stimulation (basal cortisol: 2.42 μg/dL, after stimulation: 3.29 μg/dL – normal response after 60 min should have been >20 μg/dL). Oestradiol is undetectable, but LH and FSH are not as high as typical for postmenopausal women.

? **What kind of diseases should be considered?**

✓ Our first thought for a patient with hypertension and hypokalaemia should be primary aldosteronism, but this can be excluded based on the low aldosterone level. Ectopic ACTH syndrome in severe forms could also result in hypertension and hypokalaemia

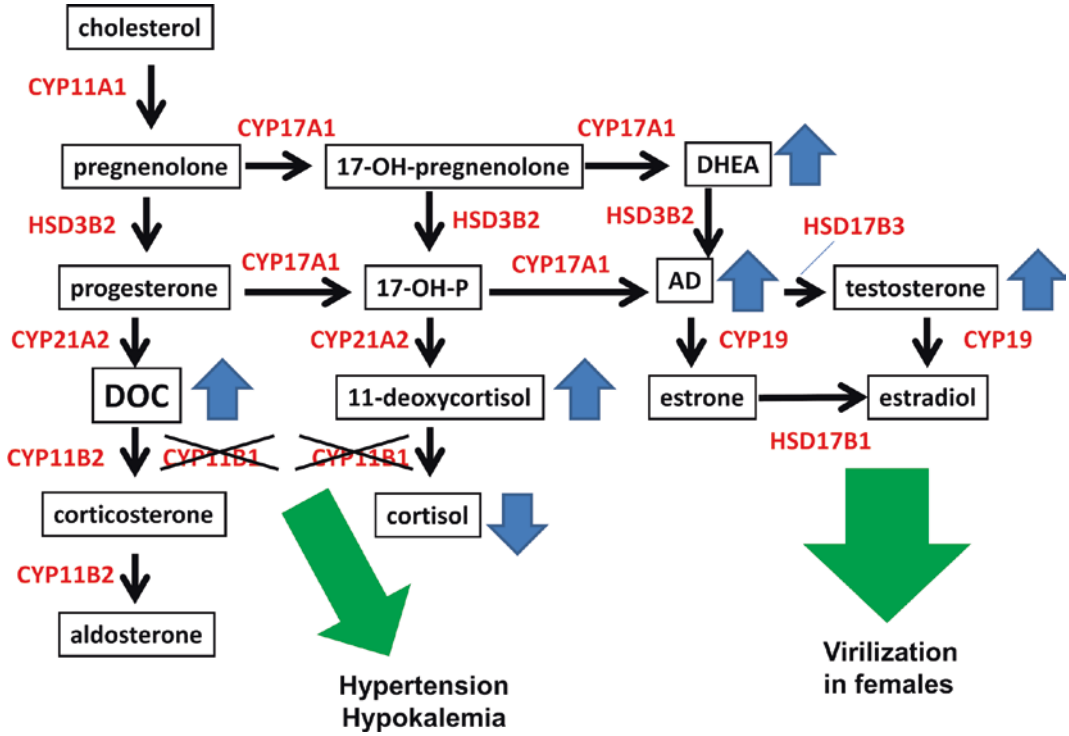

Fig. 35.2 Pathogenesis of 11β-hydroxylase (CYP11B1) deficiency. CYP11B1 deficiency leads to decreased cortisol, but the overproduction of DOC and corticosterone results in hypertension and hypokalaemia (simplified overview of steroid hormone production). Similarly to 21-hydroxylase deficiency, androgens are overproduced, resulting in virilization in females. CYP11A1 cholesterol side chain cleavage enzyme (catalysing the rate-limiting enzymatic step in steroid biosynthesis), CYP11B1 cortisol synthase, CYP11B2 aldosterone synthase, CYP19 aromatase, CYP21A2 21-hydroxylase, HSD17B 17β-hydroxylase, 17-OHP 17-hydroxy-progesterone, AD androstenedione

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due to the mineralocorticoid action of excess cortisol, but cortisol would be certainly high in this case and thus this can be excluded, as well. Overproduction of a non-aldosterone mineralocorticoid (e.g. corticosterone or DOC) might also possible, for example by a tumour or enzyme deficiency. Regarding the patient's history, the raromenorrhoea and secondary amenorrhoea together with the suspicion of mineralocorticoid excess, a steroid enzyme deficiency can be suspected.

Very rare enzyme deficiencies such as apparent mineralocorticoid excess (AME) due to mutations of type 2 11β-hydroxysteroid dehydrogenase (HSD11B2) could also result in mineralocorticoid excess. The pathomechanism of AME is similar to that of mineralocorticoid excess due to ectopic ACTH syndrome or other forms of severe hypercortisolism, since cortisol can bind the mineralocorticoid receptor with high affinity, and to prevent this under normal conditions, cortisol is metabolized to cortisone by HSD11B2 in aldosterone-responsive tissues. If cortisol is produced in such excess that the capacity of HSD11B2 is exhausted, or HSD11B2 is itself non-functional as in AME, cortisol produces mineralocorticoid effects with hypokalaemia and hypertension. In AME, the cortisol/cortisone ratio is high and aldosterone is low. AME, however, is not associated with any alterations of sex hormones, so it should not be considered in this case.

The morphology of the adrenals should be investigated to exclude an adrenal tumour that very rarely might secrete a non-aldosterone mineralocorticoid. What kind of imaging should be performed?

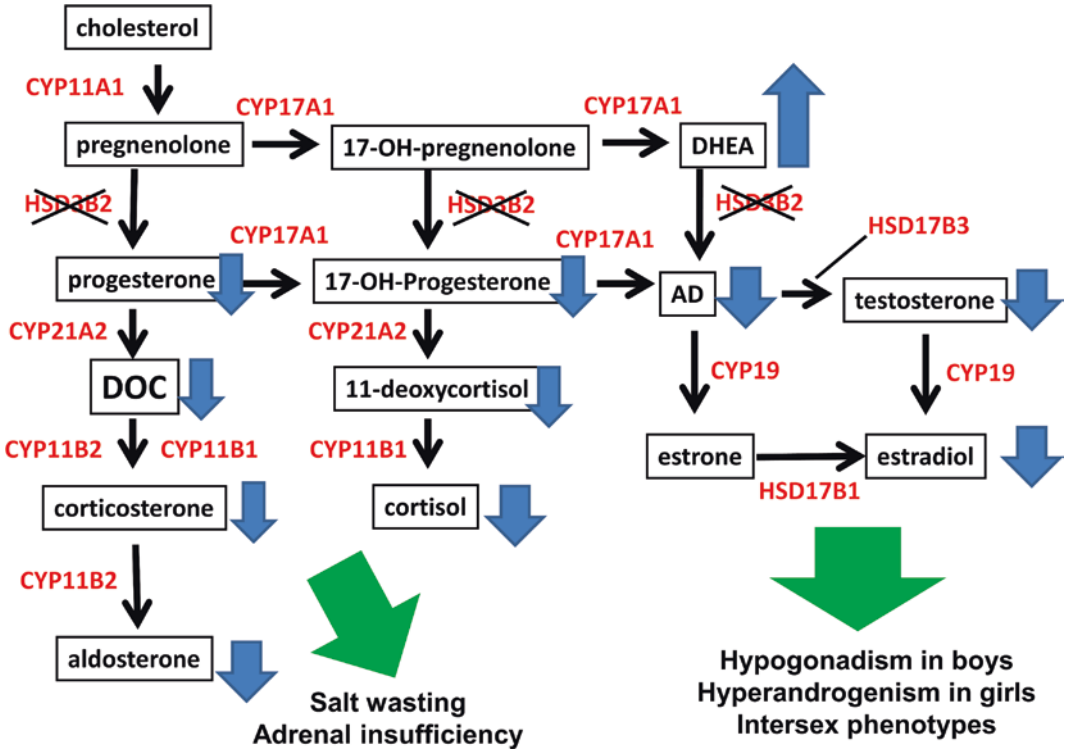

Fig. 35.3 Pathogenesis of 3β-hydroxysteroid dehydrogenase 2 (HSD3B2) deficiency. Lack of HSD3B2 leads to lack of cortisol and aldosterone, resulting in adrenal insufficiency and salt wasting (simplified overview of steroid hormone production). Among sex steroids, only DHEA (dehydroepiandrosterone) is overproduced, whereas all other sex steroids including more potent androgens and oestradiol are suppressed. These alterations lead to virilization in girls, but primary hypogonadism in boys, altogether intersex phenotypes (disorder of sexual differentiation, DSD) in both sexes. CYP11A1 cholesterol side chain cleavage enzyme (catalysing the rate-limiting enzymatic step in steroid biosynthesis), CYP11B1 cortisol synthase, CYP11B2 aldosterone synthase, CYP19 aromatase, CYP21A2 21-hydroxylase, HSD17B 17β-hydroxylase, AD androstenedione

Computed tomography (CT) is the imaging of choice. The left adrenal was hyperplastic (Fig. 35.4), and there was a large multilocular cystic tumour originating most probably from the right ovary. The morphology of the uterus also seemed abnormal.

Which further hormonal tests should be performed?

Detailed analysis of adrenal corticosteroids can be proposed to measure the levels of mineralocorticoids and sex steroids and their precursors. Table 35.2 summarizes the levels of further hormones.

The panel shows that the concentrations of adrenal androgens including androstenedione, DHEA and DHEAS are very low, whereas corticosterone, DOC and progesterone exhibit very high serum concentrations.

A deficiency of a steroid biosynthetic enzyme can be suspected. What features should be taken into account for differential diagnosis?

Table 35.3 presents the most important symptoms and hormonal changes in different forms of steroidogenic enzyme deficiencies leading to congenital adrenal hyperplasia. The table does not include all rare forms of CAH such as POR (p450 oxidoreductase deficiency), lipoid congenital adrenal hyperplasia (leading to the deficiency of all steroid hormones) and

Table 35.1 Results of the first hormonal screen

Hormone	Result	Normal range
Cortisol	2.29 μg/dL/61.8 nmol/L	8.00–25.00 μg/dL/216–675 nmol/L
ACTH	331.5 pg/mL	7.2–63.3 pg/mL
Aldosterone	<3 ng/dL	7–15 ng/dL
Renin activity	0.46 ng/mL/h	0.2–2.8 ng/mL/h
LH	13.96 IU/L	2.4–12.6 Follicular phase 14.0–95.6 Ovulatory phase 1.0–11.4 Luteal phase 7.7–58.5 Postmenopausal phase
FSH	12.97 IU/L	3.5–12.5 Follicular phase 4.7–21.5 Ovulatory phase 1.7–7.7 Luteal phase 25.8–134.8 Postmenopausal phase
E2	<10.0 pg/mL	24.5–196 Follicular phase 66.1–411 Ovulatory phase 40.0–261 Luteal phase <10–39.2 Postmenopausa
Prolactin	9.35 ng/mL	1.39–24.20 ng/ml

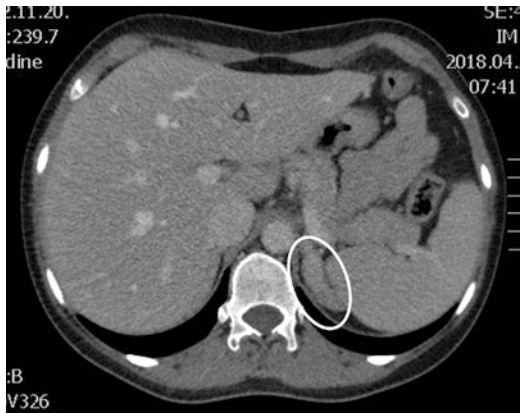

Fig. 35.4 Enlarged hyperplastic left adrenal on the CT of the patient. The right adrenal is normal

CYP11A1 deficiency, which have predominantly paediatric relevance.

Both 17α-hydroxylase/17,20-lyase and 11β-hydroxylase deficiencies lead to hypertension and hypokalaemia, but the latter would lead to virilization in females and correspondingly elevated androgens.

Regarding the high DOC and corticosterone concentrations, high progesterone, low aldosterone, low androgen and oestrogen levels, 17α-hydroxylase/17,20-lyase deficiency can be suspected. However, a complete form of this deficiency would result in primary amenorrhoea and sexual infantilism. It is thus most probably a partial form of the disease, as our patient has normal female phenotype, but secondary amenorrhoea. A complete 17α-hydroxylase/17,20-lyase deficiency in males could result in severe disorders of sexual differentiation leading to a female phenotype in a genetically male with 46,XY karyotype.

Is a genetic diagnosis warranted?

17α-Hydroxylase/17,20-lyase deficiency is inherited as an autosomal recessive trait similarly to all other forms of congenital adrenal hyperplasia. Mutations of the CYP17A1 gene are usually found in the disease. By sequencing the CYP17A1 alleles of our patient, a compound hetero-

Table 35.2 Results of further hormone measurements

Hormone	Result	Normal range
Androstenedione	<10 ng/dL	80–280 ng/dL
Dehydroepiandrosterone (DHEA)	<50 ng/dL	260–800 ng/dL
Dehydroepiandrosterone sulphate (DHEAS)	<0.1 μg/dL	61–394 μg/dL
Progesterone	1336 ng/mL	Follicular phase <0.9 ng/mL Luteal phase 1.8–24 ng/mL
Testosterone	<0.01 ng/mL	0.06–0.82 ng/mL
Corticosterone	35,550 ng/dL	226–1077 ng/dL
Deoxycorticosterone (DOC)	245 ng/dL	2–19 ng/dL

Table 35.3 Differential diagnosis of congenital adrenal hyperplasia forms based on symptoms and hormone alterations

Deficiency of	Main symptoms	Main hormonal alterations
21-hydroxylase	Salt wasting (hypotension, hyperkalaemia), hyperandrogenism	Cortisol ↓, ACTH ↑ 17-OH-progesterone ↑, androstenedione ↑
17α-hydroxylase/17,20-lyase (CYP17A1)	Hypertension, hypokalaemia, disorders of sexual differentiation (sexual infantilism in females, amenorrhoea, infertility, undervirilization or complete female phenotype in males)	Cortisol ↓, ACTH ↑ DOC ↑, corticosterone ↑, aldosterone ↓, progesterone ↑, androstenedione ↓, DHEA ↓, oestrogen ↓
11β-hydroxylase (CYP11B1)	Hypertension, hypokalaemia, hyperandrogenism in females	Cortisol ↓, ACTH ↑ DOC ↑, corticosterone ↑ Androstenedione ↑, DHEA ↑
3β-hydroxysteroid dehydrogenase 2 (HSD3B2)	Hypotension, hyperkalaemia, disorders of sexual differentiation (virilization in females, hypogonadism in males)	Cortisol ↓, ACTH ↑ Aldosterone ↓ DHEA ↑, androstenedione ↓ Testosterone ↓, oestrogen ↓

zygosity (two different mutations on the two alleles of the gene) was established. TGC22TGG (C22W, rs762563) and CGA239CAA (R239Q, rs773278607) mutations were found, which are already known pathogenic variants of the disease. As a compound heterozygosity, it can be supposed that the patient inherited a defective allele from each parent, and the parents are thus heterozygous for the CYP17A1 deficiency and healthy. Only the mother was available for genetic diagnosis, and she was found to have only the TGC22TGG (C22W, rs762563) mutation on one allele.

What kind of treatment should be proposed?

As in all forms of congenital adrenal hyperplasia, corticosteroid substitution to lower ACTH is a mainstay of treatment. Moreover, mineralocorticoid excess can be treated by antagonists of the mineralocorticoid receptor, that is, spironolactone or eplerenone.

Should we use spironolactone or eplerenone in this case?

Spironolactone is more potent, but having affinity for the androgen receptor, as well, it can cause impotence and gynaecomastia in men. As our patient is a female, eplerenone would have no indication.

Treatment Outcome

We have introduced a daily 20 mg hydrocortisone (15 mg in the morning, 5 mg in the afternoon) and 1 × 25 mg spironolactone, which was later raised to daily 50 mg. By this treatment, hypokalaemia disappeared, and the patient did not require antihypertensive therapy. The large multilocular cystic alteration of the ovary is also a manifestation of the disease.

Tips

- The reader is advised to read (or repeat) the chapters on Addison's disease (▶ Chap. 31) and other forms of congenital adrenal hyperplasia (21-hydroxylase deficiency: salt wasting and virilizing, late onset) (▶ Chaps. 32, 33 and 34).

Take Home Messages

- 17α-Hydroxylase/17,20-lyase deficiency is a rare form of congenital adrenal hyperplasia.
- In contrast to 21-hydroxylase deficiency, it leads to hypertension and hypokalaemia due to the overproduction steroid hormones with mineralocorticoid activity (11-deoxycorticosterone [DOC] and corticosterone).
- The production of sex steroids is decreased or absent in severe forms, resulting in amenorrhoea (primary or secondary depending on the severity of enzyme deficiency), infertility and disorders of sexual differentiation in males.
- Hormonal examinations show low cortisol, high ACTH, high corticosterone and DOC, low oestrogen, high progesterone levels.
- Treatment is based on hydrocortisone substitution and mineralocorticoid antagonists.

Suggested Reading

1. Auchus RJ. Steroid 17-hydroxylase and 17,20-lyase deficiencies, genetic and pharmacologic. J Steroid Biochem Mol Biol. 2017;165. (Pt A:71–8. https://doi.org/10.1016/j.jsbmb.2016.02.002.
2. Fontenele R, Costa-Santos M, Kater CE. 17 alpha-hydroxylase deficiency is an underdiagnosed disease: high frequency of misdiagnoses in a large cohort of Brazilian patients. Endocr Pract. 2018;24(2):170–8. https://doi.org/10.4158/ep171987.Or.
3. Hinz L, Pacaud D, Kline G. Congenital adrenal hyperplasia causing hypertension: an illustrative review. J Hum Hypertens. 2018;32(2):150–7. https://doi.org/10.1038/s41371-017-0002-5.
4. Marsh CA, Auchus RJ. Fertility in patients with genetic deficiencies of cytochrome P450c17 (CYP17A1): combined 17-hydroxylase/17,20-lyase deficiency and isolated 17,20-lyase deficiency. Fertil Steril. 2014;101(2):317–22. https://doi.org/10.1016/j.fertnstert.2013.11.011.
5. Miller WL. Mechanism in endocrinology: rare defects in adrenal steroidogenesis. Eur J Endocrinol. 2018;179(3):R125–r141. https://doi.org/10.1530/eje-18-0279.

Glucocorticoid Resistance

Nicolas C. Nicolaides and Evangelia Charmandari

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_36

Opening

Primary generalized glucocorticoid resistance (PGGR) or Chrousos syndrome is a rare endocrinologic condition, which is characterized by partial tissue insensitivity to glucocorticoids. The molecular basis of this condition has been attributed to genetic defects in the *NR3C1* gene encoding the human glucocorticoid receptor (hGR). In this chapter, the reader will get familiar with the clinical manifestations, endocrinologic evaluation, differential diagnosis, and therapeutic management of this syndrome.

Definition of the Disease

Primary generalized glucocorticoid resistance (PGGR) or Chrousos syndrome is a rare familial or sporadic condition, which affects all tissues expressing the human glucocorticoid receptor (hGR). It is characterized by generalized, partial tissue insensitivity to glucocorticoids due to inactivating point mutations, insertions, or deletions in the *NR3C1* gene. Patients with Chrousos syndrome have defective glucocorticoid negative feedback loops leading to compensatory hyperactivation of the hypothalamic-pituitary adrenal (HPA) axis. The resultant increased plasma adrenocorticotropic hormone (ACTH) concentrations cause adrenal hyperplasia and trigger the production of steroid precursors with mineralocorticoid activity (deoxy-corticosterone and corticosterone) and adrenal androgens (androstenedione, dehydroepiandrosterone [DHEA] and DHEA-sulfate [DHEAS]). Therefore, patients with this condition may be asymptomatic or may present with symptoms, signs, and laboratory findings suggestive of mineralocorticoid excess (hypertension and/or hypokalemic alkalosis) and/or androgen excess (ambiguous genitalia at birth in karyotypic females, hirsutism, acne, precocious puberty, male-pattern hair loss and reduced fertility in both sexes, menstrual irregularities and oligo-anovulation in women, and oligospermia in men). In addition, some patients may complain of profound anxiety and depression because of the increased production of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP). Moreover, patients may report chronic fatigue, which might indicate incomplete compensation by the elevated concentrations of cortisol in resistant glucocorticoid-target tissues, including the skeletal muscles or the central nervous system.

Case Presentation

A 30-year-old woman presented with a long-standing history of acne, hirsutism, diffuse alopecia, profound anxiety, excessive fatigue, and irregular menstrual cycles. She had no clinical manifestations suggestive of Cushing's syndrome. Endocrine evaluation showed increased 08:00 h plasma ACTH (207 pg/mL, normal range [nr] < 52 pg/mL), serum cortisol (26 μg/dL, nr: 8–25) and androstenedione (252 ng/dL, nr: <235 ng/dL) concentrations, and elevated urinary free cortisol (UFC) excretion (97–122 μg/day, nr: <50 μg/day). A pituitary magnetic resonance imaging scan was normal.

What are the features in this case that are suggestive of Chrousos syndrome?

The patient had laboratory findings suggestive of HPA axis hyperactivity (increased 08:00 h plasma ACTH and serum cortisol concentrations, and increased urinary free cortisol [UFC] excretion) without clinical manifestations of Cushing's syndrome. In addition, she presented with symptoms such as acne, hirsutism, and irregular menstrual cycles, and laboratory findings suggestive of increased adrenal androgen secretion. To exclude the diagnosis of a pituitary adenoma, a pituitary magnetic

resonance imaging scan was performed and revealed normal findings.

Which hormonal tests should be performed in this patient?

The initial endocrine evaluation of patients suspected to have Chrousos syndrome consists of measurement of the 08:00 h concentrations of plasma ACTH, serum cortisol, plasma renin activity (recumbent and upright), serum aldosterone, androgens (testosterone, androstenedione, DHEA, and DHEAS), total cholesterol, HDL, LDL, triglycerides, and fasting glucose and insulin. In addition, determination of the 24-hour UFC excretion on 2 or 3 consecutive days is crucial to set the diagnosis. However, it is worth mentioning that both the increased 24-hour UFC excretion and the elevated serum cortisol concentrations vary among patients with Chrousos syndrome due to a different degree of impairment of glucocorticoid-induced signal transduction. Therefore, serum cortisol concentrations and 24-hour UFC excretion may be, respectively, up to 7- and 50-fold higher compared with the highest value of their normal range.

Which further hormonal test should be performed?

A dexamethasone suppression test should be performed in this patient in order to evaluate the responsiveness of the HPA axis to exogenous glucocorticoids. For this test, dexamethasone should be given at increasing doses of 0.3, 0.6, 1.0, 1.5, 2.0, 2.5, and 3.0 mg per os at midnight every other day, and both serum cortisol and dexamethasone concentrations should be determined the following morning at 08.00 h to minimize the possibility of false positive results. Furthermore, dexamethasone concentrations should be measured to avoid any noncompliance to suggested treatment, or to exclude the possibility of increased metabolic clearance or reduced absorption of the administered medication. Patients with Chrousos syndrome have resistance of the HPA axis to overnight dexamethasone suppression test, as observed in the index case.

What is the differential diagnosis of Chrousos syndrome?

The differential diagnosis of Chrousos syndrome includes (i) conditions in which serum concentrations of cortisol-binding globulin (CBG) are elevated, including pregnancy and treatment with estrogens; (ii) mild forms of Cushing's disease, in which serum cortisol concentrations are increased, while plasma ACTH concentrations are normal or mildly elevated; (iii) pseudo-Cushing's states, including generalized anxiety disorder and melancholic depression; (iv) conditions associated with mineralocorticoid-induced hypertension or essential hypertension; (v) conditions causing hyperandrogenism or virilization, such as idiopathic hirsutism, polycystic ovarian syndrome, and congenital adrenal hyperplasia (CAH).

How should the patient be treated?

Patients with Chrousos syndrome are treated with high doses of mineralocorticoid-sparing synthetic glucocorticoids, such as dexamethasone (1–3 mg given once daily). The dose should be carefully titrated in order to suppress adequately the HPA axis to avoid the development of ACTH-secreting adenomas. In addition, attention should be paid to any side effects of dexamethasone (iatrogenic Cushing's syndrome).

The index case was treated with dexamethasone at a dose of 1 mg per os at night. The clinical manifestations of the condition subsided, and the concentrations of plasma ACTH and serum androgens were normalized.

Are there any molecular biology methods that confirm the diagnosis?

Dexamethasone-binding assays and thymidine incorporation assays on peripheral leu-

kocytes are needed to confirm the diagnosis of Chrousos syndrome. Dexamethasone-binding assays reveal lower affinity of the defective receptor for the ligand compared with control subjects. Thymidine incorporation assays show resistance to dexamethasone-induced suppression of phytohemaglutinin-stimulated thymidine incorporation in the patients compared with control subjects. Finally, sequencing of the coding region of the *NR3C1* gene, including the intron-exon junctions, will reveal any genetic defects such as point mutations, insertions, or deletions.

Following sequencing of the *NR3C1* gene, the patient was shown to harbor a novel heterozygous A > G substitution at nucleotide position 2177, which resulted in histidine (His, H) to arginine (Arg, R) substitution at amino acid position 726 in exon 8 (c.2177A > G, p.H726R) in helix 10 of the ligand-binding domain (LBD) of the glucocorticoid receptor.

How does the mutant receptor hGRαH726R cause generalized glucocorticoid resistance in the patient?

The tremendous progress of molecular and structural biology has enabled us to gain a better understanding of the molecular mechanisms and conformational alterations through which the mutant glucocorticoid receptors cause generalized glucocorticoid resistance. These mechanisms include (i) the transcriptional activity of the mutant receptors; (ii) the ability of the heterozygous mutant receptors to exert a dominant negative effect upon the wild-type receptor; (iii) the concentrations of the mutant receptors and their affinity for the ligand; (iv) the subcellular localization of the mutant receptors and their nuclear translocation following exposure to the ligand; (v) the ability of the mutant receptors to bind to glucocorticoid response elements (GREs); (vi) the in vitro interaction of the mutant receptors with the glucocorticoid receptor-interacting protein 1 (GRIP1) coactivator, which belongs to the p160 family of nuclear receptor coactivators and plays an important role in hGRα-mediated transactivation of glucocorticoid-responsive genes; (vii) the motility of the mutant receptors inside the nucleus; (viii) the ability of the mutant receptors to transrepress the NF-κB signaling pathway; and (ix) structural biology studies.

Compared with the wild-type receptor, the mutant receptor hGRαH726R of the index case demonstrated reduced ability to transactivate glucocorticoid-responsive genes and to transrepress the nuclear factor-κB signaling pathway. In addition, it displayed 55% lower affinity for the ligand and a four-fold delay in cytoplasmic-to-nuclear translocation, and interacted with the GRIP1 coactivator in vitro mostly through its activation function-1 domain. Finally, a three-dimensional molecular modeling study of the H726R mutation showed a significant structural shift in the rigidity of helix 10 of the receptor causing reduced flexibility and decreased affinity of the mutant receptor for ligand binding.

Tips

The reader is advised to read the chapters on hypercortisolism (Cushing's disease; ▶ Chap. 3) and adrenal Cushing's syndrome (▶ Chap. 27). Thyroid hormone resistance syndrome (▶ Chap. 20) and complete androgen insensitivity (▶ Chap. 43) discuss resistance syndromes linked to other steroid hormone receptors.

Take Home Messages

- Primary generalized glucocorticoid resistance or Chrousos syndrome is a rare endocrinologic condition, which is

characterized by generalized, partial end-organ resistance to glucocorticoids.
- The molecular basis of the condition has been attributed to genetic defects in the *NR3C1* gene.
- Patients with Chrousos syndrome have defective glucocorticoid negative feedback loops leading to compensatory hyperactivation of the HPA axis, and may be asymptomatic or may present with clinical manifestations and laboratory findings suggestive of mineralocorticoid and/or androgen excess.
- A detailed endocrine evaluation should be performed with particular emphasis on the determination of serum cortisol concentrations and 24-hour UFC excretion on 2 or 3 consecutive days.
- Affected patients display resistance of the HPA axis to dexamethasone suppression, which may vary depending on the severity of the condition.
- The diagnosis of Chrousos syndrome is confirmed by dexamethasone-binding assays, thymidine incorporation assays, and sequencing of the coding region of the *NR3C1* gene, including the intron/exon junctions.
- Patients with Chrousos syndrome are treated with high doses of mineralocorticoid-sparing synthetic glucocorticoids, such as dexamethasone, which activate the mutant and/or wild-type hGRα, and suppress the endogenous secretion of ACTH.
- Molecular and structural biology methods have enabled the investigation of the molecular mechanisms and conformational alterations through which the mutant glucocorticoid receptors cause glucocorticoid resistance.

Further Reading

1. Charmandari E, Kino T. Chrousos syndrome: a seminal report, a phylogenetic enigma and the clinical implications of glucocorticoid signaling changes. Eur J Clin Investig. 2010;40:932–42. https://doi.org/10.1111/j.1365-2362.2010.02336.x.
2. Charmandari E, Kino T, Chrousos GP. Primary generalized familial and sporadic glucocorticoid resistance (Chrousos syndrome) and hypersensitivity. Endocr Dev. 2013;24:67–85. https://doi.org/10.1159/000342505.
3. Nicolaides N, Lamprokostopoulou A, Sertedaki A, Charmandari E. Recent advances in the molecular mechanisms causing primary generalized glucocorticoid resistance. Hormones (Athens). 2016;15(1):23–34. https://doi.org/10.14310/horm.2002.1660.
4. Nicolaides NC, Charmandari E. Novel insights into the molecular mechanisms underlying generalized glucocorticoid resistance and hypersensitivity syndromes. Hormones (Athens). 2017;16(2):124–38. https://doi.org/10.14310/horm.2002.1728.
5. Nicolaides NC, Charmandari E. Glucocorticoid resistance. Exp Suppl. 2019;111:85–102. https://doi.org/10.1007/978-3-030-25905-1_6.
6. Nicolaides NC, Chrousos GP. Bilateral adrenal hyperplasia and NR3C1 mutations causing glucocorticoid resistance: is there an association? Eur J Endocrinol. 2018;179(5):C1–4. https://doi.org/10.1530/EJE-18-0471.
7. Nicolaides NC, Geer EB, Vlachakis D, et al. A novel mutation of the hGR gene causing Chrousos syndrome. Eur J Clin Investig. 2015;45:782–91. https://doi.org/10.1111/eci.12470.
8. Velayos T, Grau G, Rica I, Pérez-Nanclares G, Gaztambide S. Glucocorticoid resistance syndrome caused by two novel mutations in the NR3C1 gene. Endocrinol Nutr. 2016;63(7):369–71. https://doi.org/10.1016/j.endonu.2016.03.010.
9. Vitellius G, Fagart J, Delemer B, et al. Three novel heterozygous point mutations of NR3C1 causing glucocorticoid resistance. Hum Mutat. 2016;37(8):794–803. https://doi.org/10.1002/humu.23008.
10. Vitellius G, Lombes M. Genetics in endocrinology: glucocorticoid resistance syndrome. Eur J Endocrinol. 2020;182(2):R15–27. https://doi.org/10.1530/EJE-19-0811.

Pheochromocytoma

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Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_37

Opening

In this chapter, the reader will get acquainted with the clinical features, diagnosis, and treatment of pheochromocytomas and paragangliomas.

Definition of the Disease

Pheochromocytoma is a neuroendocrine tumor arising from the adrenal medulla (80%). When the tumor is located outside the adrenals, in the chromaffin tissue of the sympathetic ganglia (20%), it is called paraganglioma.

Tumors located in the parasympathetic ganglia of the head and neck region are also called paragangliomas (head and neck paragangliomas, HNPGL). These later do not generally release catecholamines (CA), at variance with the sympathetic tumors (PPGL: pheochromocytoma/paraganglioma). PPGL have an incidence of two to eight cases/million/year and cause hypertension in about 0.1% of hypertensives. They do not show gender preference. The mean age of presentation is 40–50 years, but people at every age can be affected. PPGL/HNPGL are the most hereditable tumors; germ-line mutations causing familial forms account for 40% of cases. In 60% of cases, PPGL/HNPGL are sporadic. The familial forms occur at an earlier age.

Since PPGL can be associated with very serious, potentially fatal cardiovascular complications, its diagnosis and treatment is a very important issue.

Case Report

A young male, aged 20 years, consults his general practitioner for the occurrence of headache during physical activity. His ambulatory blood pressure is 160/120 mmHg. The family history was negative for hypertension. His doctor requests blood tests for the differential diagnosis of secondary hypertension including the measurement of urinary metanephrines which resulted as follows: metanephrine (MN) 37 µg/24 hours (normal range: 70–320) and normetanephrine (NMN) 1921 µg/24 hours (normal range: 40–390). This result is diagnostic for the occurrence of a PPGL.

Was the clinical picture diagnostic for the occurrence of a PPGL?

No, the clinical picture was only suggestive of a secondary hypertension which, although rarely (about 0.1%), includes PPGL. The clinical presentation of PPGL is extremely variable (Table 37.1) ranging from sustained and paroxysmal hypertension (associated mostly to palpitations, headache, sweating, and anxiety) to mild continuous hypertension (not different from essential hypertension) to absence of symptoms and normotension (up to 20%).

Table 37.1 Signs and symptoms in patients with PPGL and their approximative frequencies

Signs and symptoms	Frequencies (%)
Headache	60–80
Tachycardia/palpitations	50–70
Sweating	40–60
Anxiety	20–40
Sustained hypertension	50–60
Paroxysmal hypertension	40–60
Pallor	35–45
Nausea	20–25
Weight loss	20–40
Orthostatic hypotension	10–20
Glucose intolerance/diabetes mellitus	40–50
Flushing	10–20
Vertigo	10–20
Dyspnea	10–20

Box 37.1 Pathological Conditions Mimicking PPGL – Differential Diagnosis

- Hyperthyroidism
- Hypoglycemia
- Medullary thyroid carcinoma
- Mastocytosis
- Menopausal syndrome
- Panic disorder
- Migraine
- Carcinoid syndrome
- Ischemic heart disease
- Heart failure
- Stroke
- Arrhythmias
- Epilepsia
- Drugs (monoamino-oxidase inhibitors, sympathomimetics, clonidine withdrawal, and cocaine)

The most typical symptoms of PPGL are seen with adrenal pheochromocytomas secreting adrenaline. Many PPGL are diagnosed after an incidental discovery of an adrenal or extra-adrenal abdominal mass (incidentaloma). Even in the presence of all the above-mentioned paroxysmal symptoms, the diagnosis of PPGL is not possible on the clinical ground as these symptoms can occur in other more frequent circumstances (▶ Box 37.1), such as panic disorder.

How to diagnose a PPGL?

PPGL are diagnosed by laboratory results. Almost all PPGL synthesize and release CA and their metabolites. Pheochromocytomas release noradrenaline (NA) and sometimes adrenaline (A), while abdominal or thoracic PGL release only NA and sometimes dopamine (DA). The compounds to be assayed are the metanephrines (MNs), the methylated derivatives of CA (metanephrine for A, normetanephrine [NMN] for NA, and eventually methoxytyramine for DA). Metanephrines (MNs) can be measured either in blood or in urine. MNs are the recommended assay because they have the highest sensitivity (about 98%), higher than the CA assay (85%), thus showing a lower number of false negative. The higher sensitivity of MNs is due to their continuous release by the tumor tissue, where the enzyme (catechol-O-methyltransferase, COMT) transforms CA into MNs, while CA are only sporadically released. MN values two- to threefold higher than the upper normal limits are diagnostic for a PPGL. Normal values practically exclude the presence of a PPGL. MNs measurement, especially NMN (normetanephrine), may give false positive results in patients with chronic activation of the sympathetic system by heart failure, decompensated liver cirrhosis, renal failure, pulmonary insufficiency, in subjects affected by sleep apnea syndrome, or in subjects assuming drugs such as antidepressants. Some centers use the clonidine test to differentiate non-PPGL-associated NMN-elevation due to increased sympathoadrenal activity, as the central α2-receptor agonist clonidine inhibits central sympathoadrenal activity without affecting PPGL. A reduction of more than 50% of plasma NMN after 0.3 mg oral clonidine is diagnostic.

In addition to CA metabolites, the general neuroendocrine tumor marker serum chromogranin A (CgA) is usually also elevated in PPGL patients.

From which body fluid should MNs be determined? (urine vs. plasma)

MNs can be measured in plasma or in urine. Plasma-free MNs, combined with the dopamine metabolite 3-methoxytyramine, offer a slightly higher sensitivity (99% vs. 95%) and a higher specificity (96% vs. 89%) than that of urinary deconjugated MNs.

When measuring plasma MNs, blood sampling should be performed in standardized conditions, preferably while fasting and in supine position, avoiding environmental stress. Samples should be drawn in heparinized tubes kept on ice to avoid degradation.

How should urine sampling be performed?

For measurement of urinary MNs, containers do not need additives as long as the urine sample is acidified (pH 4) before storage. Simultaneous measurement of urinary creatinine excretion is useful to verify complete 24-hour urine collection.

Why is it important to diagnose a PPGL?

Chronic exposure to high levels of CA is a cardiovascular and metabolic risk, possibly causing hypertension, myocardial hypertrophy and insufficiency, glucose intolerance or diabetes mellitus. The occurrence of massive abrupt release of CA may cause severe hypertensive spurts and can lead to myocardial infarction, pulmonary edema, ictus, and death. Cardiomyopathy might also occur, that can be acute (e.g., tako-tsubo resembling acute myocardial infarction) or chronic. Hypertensive crises can be spontaneous or induced by causes (Table 37.2) such as cold, physical exercise, or drugs.

Table 37.2 Factors reported to induce hypertensive crises in patients with PPGL

Mechanical	Palpation of abdomen, physical exercise, change of posture, cough or sneezing, defecation, sexual intercourse, delivery, surgery, invasive diagnostic procedures (venous sampling, arteriography, and fine needle biopsy), and micturition (in case of bladder PPGL)
Drugs	Histamine, tyramine, glucagon, alcohol, nicotine, sympathetic amines, metoclopramide, chlorpromazine, tricyclic antidepressants, monoamine oxidase inhibitors, steroids, non-cardiac selective ß-adrenergic receptor blockers, naloxone, saralasin, theophylline, caffeine, chemotherapeutic agents, and neuromuscular blocking agents
Others	Pain, emotional stress, and cold exposure

Case Report (Continued)

The patient was referred to a reference center where the patient was proposed for genetic testing which was performed after patient's consent. The test, performed on blood lymphocytes DNA, revealed the presence of a germ-line mutation (Q109X) in the gene encoding the D subunit of the succinate-dehydrogenase (*SDHD*) or mitochondrial complex II, accounting for the presence of familial paragangliomatosis type 1 (PGL1).

What is the clinical presentation of HNPGL?

HNPGL do not generally release CA. They very rarely release DA. Therefore, they do not cause systemic clinical signs but only local symptoms due to regional nerve compression. They can affect any of the parasympathetic ganglia (carotid glomus, laryngeal, vagal, jugular, tympanic ganglia). They can cause dysphagia, tinnitus, anisocoria, deafness, and vocal impairment, or they can be incidentally discovered during a radiological exam of the head and neck regions. Only the largest HNPGL present as lateral cervical masses.

Is it important to genotype patients affected by PPGL?

In view of the high prevalence of familial forms (about 40%), genotyping is recommended in every patient with PPGL. The diagnosis of a familial form is important for the patient and her/his family members. In fact, the patient, as well as the family members found to be carriers of the mutation, has to be enrolled in a life-long follow-up for the early diagnosis of recurrent or primary PPGL and, depending on the gene mutation, of the other eventually associated syndromic lesions. There are many susceptibility genes for PPGL/HNPGL. The main genes and associated syndromes are presented in Table 37.3.

Case Report (Continued)

The family pedigree is shown in Fig. 37.1. The father (52 years old), the grandfather (72 years old), and the grandfather's brother (74 years old) were found to carry the mutation. None of them referred symptoms nor were found hypertensive. The laboratory test showed normal MN and an almost twofold increase of the father's urinary NMN (755 μg/24 hours), while both urinary NMN and MN were found normal in both the grandfather and his brother. These results strongly suggest the presence of a PPGL in the father and exclude its occurrence in the two older subjects.

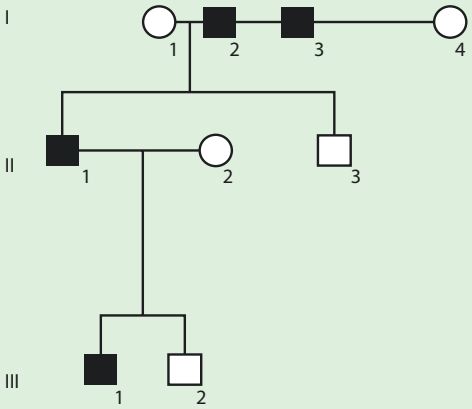

Fig. 37.1 Patient's family pedigree. Patient (III1); Patient's father (II1); Patient's grandfather (I2), and his brother (I3). Squares: males. Circle: females. Black symbols: mutated patients. White symbols: non-mutated subjects

Why the two oldest family members, although mutation carriers, had not developed the disease?

The explanation for that is that the *SDHD* gene is maternally imprinted, and therefore, only patients who receive the mutation from the father develop the disease (genomic imprinting is an epigenetic process whereby the paternal and maternal alleles of the gene are differentially expressed).

Which steps are needed after the laboratory positive test?

Only after biochemical confirmation, the PPGL must be localized. About 85% of PPGL are located in the abdomen and about 80% of these in the adrenals. Computed tomography (CT) and magnetic resonance imaging (MRI) are the recommended initial anatomic imaging modalities. Once localized the lesion(s), the decision whether further whole-body anatomic and functional studies are needed depends mainly on the likelihood for metastasis. Functional imaging includes ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy and the positron emission tomography hybridized with CT (Positron Emission Tomography (PET)/CT) using different tracers as fluorodeoxyglucose (^{18}F-FDG), F-fluorodopa (^{18}F-FDOPA), and Gallium (^{68}Ga)-somatostatin analogs. ^{123}I-MIBG scintigraphy is the most widely used in view of its availability, low cost, and low radiation exposure, and it is recommended in case of suspected PPGL malignancy (see below), being preliminary to radiotherapy of metastatic PPGL with ^{131}I-MIBG. Similarly, (^{68}Ga)-DOTATATE PET/CT is preliminary to radiotherapy with ^{177}Lu-DOTATATE. PET/CT is generally employed in disease evaluation, treatment plan, and assessment of tumor response.

What are the typical imaging features of adrenal pheochromocytoma by CT and MRI?

At CT adrenal pheochromocytoma appears as round masses of different sizes, sometimes homogeneous, more often inhomogeneous for the presence of hemorrhagic spots. Their density is higher than 10 Hounsfield Units (HU), and the contrast medium washout is less than 50%.

At MRI, because of their rich vascularization, adrenal pheochromocytomas typically appear hyperintense at T2-weighted scans.

Table 37.3 Main susceptibility genes for PPGL/HNPGL and their main characteristics

Gene	Syndrome	Most frequent lesions	Associated lesions	PPGL/HNPGL malignancy	Genetic transmission
VHL	Von Hippel-Lindau	Pheo (bilateral)	HMG, RCC, PC, EST	Low	AD
RET	MEN2a MEN2b	Pheo (bilateral)	MTC, HPT, LCE MTC, MH, MMN	Low	AD
NF1	Neurofibromatosis	Pheo (bilateral)	MN, CLS, LN, OG	Low	AD
SDHB	FP 4	Abdominal PPGL (multiple)	GIST, RCC, PA	High	AD
SDHD	FP 1	HNPGL (multiple)	GIST, RCC, PA	Intermediate	AD/PT
SDHC	FP 3	HNPGL		N.k.	AD
SDHA	FP 5	HNPGL		N.k.	AD
SDHA2F	FP 2	HNPGL		N.k.	AD/PT
TMEM127	Familial Pheo	Pheo (bilateral)		Low	AD
MAX	Familial Pheo	Pheo (bilateral)		Intermediate/ high	AD
FH	HLRCC	Abdominal PPGL	UL, RCC	High	AD

MEN2 multiple endocrine neoplasia type 2a/b, *FP* familial paragangliomatosis, *HLRCC* hereditary leiomyomatosis–renal cell carcinoma, *Pheo* pheochromocytoma, *HNPGL* head/neck paraganglioma, *HMG* hemangioblastomas (cerebral/retinal), *RCC* renal cell carcinoma, *PC* pancreatic cysts, *EST* endothelial sac tumors *MTC* medullary thyroid carcinoma, *HPT* hyperparathyroidism, *LCE* lichen cutaneous erythematous, *MH* marfanoid habitus, *MMN* multiple mucosal neuromas, *MN* multiple neurofibroma, *CLS* cafè-au-lait spots, *LN* Lisch nodules, *OG* Optic glioma, *GIST* gastrointestinal stromal tumors, *PA* pituitary adenoma, *UL* uterine leiomyomata, *n.k.* not known, *AD* autosomal dominant, *AD/PT* autosomal dominant with paternal transmission

Case Report (Continued)

The patient and his father underwent an abdomen CT which showed the presence of a 5 cm left adrenal mass in the patient (Fig. 37.2) and a 2 cm left pararenal PPGL in the father (Fig. 37.3a). In view of the clinical picture associated to *SDHD* mutation, both patients underwent also a head and neck MRI which was negative for the patient while showed a 2 cm bilateral carotid body PGL (glomus tumor) in the father (Fig. 37.3b).

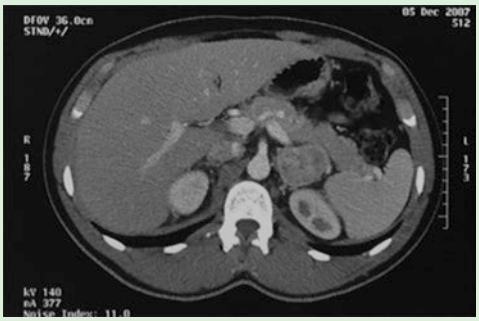

Fig. 37.2 Patient's abdominal CT showing a 5 cm large left adrenal mass

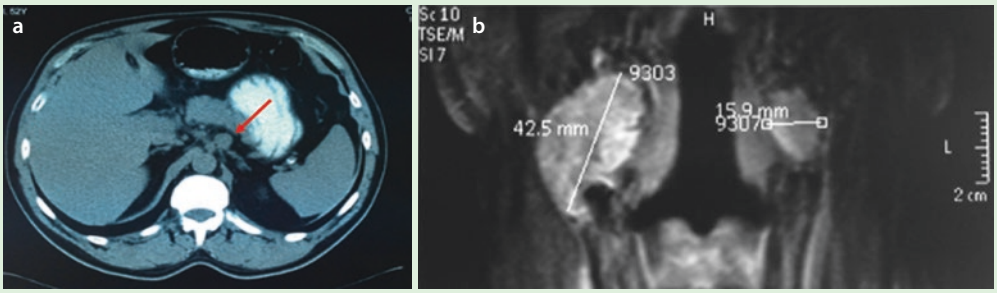

Fig. 37.3 Abdominal CT imaging of the patient's father **a** showing a 2 cm left para-adrenal mass, and neck MRI **b** showing a bilateral carotid body tumor

What is the therapy for PPGL and HNPGL?

The therapy of choice for PPGL is the removal of the lesion by an experienced surgeon. For PPGL less than 6 cm in diameter, the recommended approach is laparoscopic. In case of bilateral pheochromocytoma or in patients affected by unilateral pheochromocytoma due to syndromes like von Hippel-Lindau syndrome (VHL, ▶ Chap. 52), multiple endocrine neoplasia type 2 (MEN2, ▶ Chap. 51), and neurofibromatosis type 1 (NF1) characterized by the occurrence of bilateral lesions, the recommended approach is adrenal sparing surgery, to avoid chronic adrenocortical insufficiency. Before PPGL, removal patients must be medically prepared. The drugs of choice are α-receptor antagonists associated or not to other drugs like β-receptor antagonists (β-blockers), calcium channel blockers, fluids. β-receptor antagonists must not be administered before administration of α-receptor antagonists has been ensued. Diuretics are contraindicated. The rationale for the use of α-receptor antagonists is to limit hypertensive crises before and during surgery and to limit severe dreadful hypotensive crises once the tumor has been removed. In fact,

in the absence of medical therapy, the rapid disappearance of CA from the blood may cause a massive vasodilation worsened by the blood volume restriction due to CA vasoconstriction. An adequate presurgical α-receptor antagonist therapy causes a controlled vasodilation and volume expansion, limiting the hypotensive crises which, in addition, do not respond to NA infusion because of the α-receptor down regulation caused by the chronic exposure of vessels to high levels of CA. At present, the most used α-receptor antagonists are phenoxybenzamine and doxazosin. Their characteristics are reported in Table 37.4.

Another drug, mostly used in the past in metastatic cases, is α-methylparathyrosine, an inhibitor of tyrosine-hydroxylase, the limiting enzyme in the synthesis of CA. It reduces the synthesis of CA released by the PPGL but also of the CA secreted by the sympathetic system, thus causing important side effects like profound orthostatic hypotension.

Table 37.4 Medical treatment of patients with pheochromocytoma/paraganglioma: characteristics of the most used α-blocking drugs

Phenoxybenzamine	Doxazosine
α-receptor antagonist	α-receptor antagonist
Non-selective: blocks α1- and α2-receptors	Selective: Blocks α1-receptors
Non-competitive	Competitive
Half-life: 24 hours	Half-life: 20 hours
Capsules: 10 mg	Tablets: 1 or 2 or 4 or 8 mg
Side effects: tachycardia, postural hypotension, nasal stiffness, impaired ejaculation	Side effects: postural hypotension

The therapy of HNPGL is still a matter of debate. The ideal approach would be surgical removal by an experienced surgeon, but even the most experienced cannot avoid permanent side effects caused by the complete removal of vagal, jugular, and tympanic tumors. The surgical approach can be decided for sporadic glomus tumors. For familial glomus tumors, very often bilateral (synchronous or metachronous), the removal of both the tumors eliminates their baroreceptor function causing an unpleasant increase in blood pressure and heart rate variability. Therefore, at present, the clinical options range from a "wait and see" behavior to a stereotactic radiosurgery using gamma-knife.

Why are β-receptor antagonists contraindicated as monotherapy in PPGL patients?

At the vascular level, ß-receptors (mainly ß2) are vasodilating and α-receptors are vasoconstricting. When stimulated by circulating CA, vasoconstriction prevails causing a rise in blood pressure. If the vasodilating component exerted by ß-receptors is blocked by an antagonist, the blood pressure increase caused by a PPGL-induced CA release is much higher and dangerous.

Case Report (Continued)

Both the patient and his father underwent laparoscopic removal of the abdominal PPGL after a seven-day therapy with doxazosine, an α-receptor antagonist. Tumor removal was uneventful and the patients were discharged on the third day after surgery. At pathology, the masses were diagnosed as PPGL. For the father's bilateral carotid body tumors, a "wait and see" strategy was consensually decided.

Can pathology determine whether a PPGL is benign or malignant?

At present, there are no definitive markers to diagnose malignancy. For PPGL, malignancy is diagnosed by the presence of metastases in tissues devoid of chromaffin cells such as lymph nodes, liver, lungs, and bones. Recently, the WHO has considered all the PPGL as potentially malignant tumors and defined them as metastatic or not. Risk factors for malignancy are large tumor size, extra-adrenal site, noradrenergic or dopaminergic biochemical profile, and mutations in *SDHB, FH,* and *MDH2* genes.

Case Report (Continued)

A control visit and measurement of urinary MNs were planned after 30 days from surgery. In both patients urinary MNs resulted in the normal range. A clinical, laboratory, and imaging follow-up was consensually decided.

How to follow up patients after surgery?

After about 15 days from tumor removal a control of plasma or urinary MNs is recommended. Normal values are consistent with a disease-free condition. The subsequent follow-up depends on the patient's genetic status. Since PPGL malignancy cannot be excluded by histological examination, patients should be followed up for at least 10 years after surgery by annual MNs measurements.

In case of a familial PPGL, a life-long clinical and laboratory follow-up is recommended. The frequency and the type of follow-up depends also on the type of mutation, being stricter for genes, like *SDHB*, associated to metastatic disease.

Tips

The reader is advised to read the following chapter on malignant paraganglioma (▶ Chap. 38) and the chapters on multiple endocrine neoplasia type 2 (▶ Chap. 51) and von Hippel-Lindau syndrome (▶ Chap. 52).

Take Home Messages

- Pheochromocytoma and Paraganglioma (PPGL) are rare neuroendocrine tumors presenting with a highly variable clinical picture and difficulties in the diagnosis.
- They are mostly localized in the adrenal glands.
- PPGL are genetically determined in about 40% of cases.
- PPGL should be suspected in case of paroxysmal or resistant hypertension, of adrenal or abdominal/thoracic incidentalomas, and with a positive family history.
- When undiagnosed, PPGL are at risk of severe cardiovascular complications.
- The diagnosis is based on laboratory results. The compounds to be assayed are plasma or urine metanephrines.
- Localization of PPGL is reached by radiological imaging, CT, and/or MRI.
- Functional imaging can be employed in selected cases, depending on location and genetic background.
- Genetic testing and counseling should be offered to every patient with PPGL.
- PPGL are rarely metastatic. Some genetic forms (*SDHB* mutation) are at higher risk.
- The therapy of PPGL is surgical, possibly using a laparoscopic approach. In case of bilateral pheochromocytoma, a sparing surgery is recommended.

- To reduce cardiovascular instability before, during, and soon after surgery, a medical therapy with α-blockers (phenoxybenzamine or doxazosine) is highly recommended.
- Patients operated for non-familial PPGL should be controlled yearly for 10 years. In case of a familial form, a life-long follow-up is recommended.

Suggested Reading

1. Crona J, Lamarca A, Ghosal S, Welin S, Skogseid B, Pacak K. Genotype-phenotype correlations in pheochromocytoma and paraganglioma. Endocr Relat Cancer. 2019;26(5):539–50. https://doi.org/10.1530/ERC-19-0024.
2. Hescot S, Curras-Freixes M, Deutschbein T, van Berkel A, Vezzosi D, Amar L, de la Fouchardière C, Valdes N, Riccardi F, Do Cao C, Bertherat J, Goichot B, Beuschlein F, Drui D, Canu L, Niccoli P, Laboureau S, Tabarin A, Leboulleux S, Calsina B, Libé R, Faggiano A, Schlumberger M, Borson-Chazot F, Mannelli M, Gimenez-Roqueplo AP, Caron P, Timmers HJLM, Fassnacht M, Robledo M, Borget I, Baudin E, European Network for the Study of Adrenal Tumors (ENS@T). Prognosis of malignant pheochromocytoma and paraganglioma (MAPP-Prono study): a European network for the study of adrenal tumors retrospective study. J Clin Endocrinol Metab. 2019;104:2367–74. https://doi.org/10.1210/jc.2018-01968.
3. Isaacs M, Lee P. Preoperative alpha-blockade in phaeochromocytoma and paraganglioma: is it always necessary? Clin Endocrinol. 2017;86:309–14. https://doi.org/10.1111/cen.13284.
4. Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo A-P, SKG G, Murad MH, Naruse M, Pacak K, Young WF Jr, Endocrine Society. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99:1915–42. https://doi.org/10.1210/jc.2014-1498.
5. Lenders JMW, Eisenhofer G, Mannelli M, Pacak K. Phaeochromocytoma. Lancet.2005;366(9486):665–75. https://doi.org/10.1016/S0140-6736(05)67139-5.
6. Lenders JW, Pacak K, Walther MM, Linehan WM, Mannelli M, Friberg P, Keiser HR, Goldstein DS, Eisenhofer G. Biochemical diagnosis of pheochromocytoma: which test is best? JAMA. 2002;287:1427–34. https://doi.org/10.1001/jama.287.11.1427.
7. Mercado-Asis LB, Wolf KI, Jochmanova I, Taïeb D. Pheochromocytoma: a genetic and diagnostic update. Endocr Pract. 2018;24:78–90. https://doi.org/10.4158/EP-2017-0057.
8. Plouin PF, Amar L, Dekkers OM, Fassnacht M, Gimenez-Roqueplo AP, Lenders JW, Lussey-Lepoutre C, Steichen O. European Society of Endocrinology Clinical Practice Guideline for long-term follow-up of patients operated on for a phaeochromocytoma or a paraganglioma. Eur J Endocrinol. 2016;174(5):G1–g10. https://doi.org/10.1530/eje-16-0033.
9. Taïeb D, Hicks RJ, Hindié E, Guillet BA, Avram A, Ghedini P, Timmers HJ, Scott AT, Elojeimy S, Rubello D, Virgolini IJ, Fanti S, Balogova S, Pandit-Taskar N, Pacak K. European Association of Nuclear Medicine Practice Guideline/Society of Nuclear Medicine and Molecular Imaging Procedure Standard 2019 for radionuclide imaging of phaeochromocytoma and paraganglioma. Eur J Nucl Med Mol Imaging. 2019;46:2112–37. https://doi.org/10.1007/s00259-019-04398-1.

Malignant Paraganglioma

Andrea Uhlyarik and Peter Igaz

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_38

Opening

The previous chapter discussed the complex issue of pheochromocytoma. In this brief chapter, malignant paraganglioma (extraadrenal pheochromocytoma) is discussed.

Definition of the Disease

Paragangliomas are rare neuroendocrine tumors arising from chromaffin tissue outside the adrenal medulla. Paragangliomas can be alternatively termed as extraadrenal pheochromocytomas, representing about 10–20% of all pheochromocytomas. Malignancy is more frequent in extraadrenal paragangliomas (20–25%) than in adrenal pheochromocytomas (5–10%).

Case Presentation

The male patient was 50 years of age when a large retroperitoneal, cystic tumor was diagnosed due to complaints of weight loss and abdominal discomfort. The tumor was successfully resected (R0). Histology of the retroperitoneal tumor showed a paraganglioma. He had hypertension since the age of 36. He was referred to our center at the age of 53 following the results of a CT scan showing tumor recurrence at the primary site along with multiple lung metastases. His blood pressure was well controlled with a combination of angiotensin converting enzyme (ACE)-inhibitor and Ca-antagonist. Bone metastases are often observed in malignant paraganglioma/pheochromocytoma, but the bone scan did not show any metastases. As bone metastases often affect the skull, regular physical examination of the head is proposed in these patients.

What kind of hormone measurements should be performed?

As discussed in more detail in the previous chapter on pheochromocytoma (▶ Chap. 37), catecholamine metabolites and chromogranin A (CgA) should be determined. ◘ Table 38.1 summarizes the results of the first hormone panel.

What can be inferred from this hormone panel (◘ Table 38.1)?

Urinary normetanephrines are very high, whereas metanephrines are normal. High metanephrines, as degradation products of adrenaline (epinephrine), are usually seen in pheochromocytomas of adrenal origin, as the production of adrenaline needs high local glucocorticoid concentration. The constellation of high normetanephrines and normal metanephrines corresponds to the extraadrenal origin of the tumor. High 3-methoxytyramine levels are often seen in metastatic pheochromocytomas. Chromogranin A (CgA), as a general marker for neuroendocrine tumors, is highly elevated.

How can we explain the well-controlled blood pressure with so high catecholamine metabolite levels?

Whereas adrenaline-secreting adrenal pheochromocytomas are typically associated with severe hypertension and characteristic symptoms of pheochromocytomas, noradrenaline secretion is usually not associated with severe hypertension. The patient's well-controlled hypertension can be explained with the lack of adrenaline secretion. Nevertheless, we introduced an alpha-blocker (doxazosine) to his hypertensive drugs, as alpha-blockers represent the mainstay of antihypertensive treatment in pheochromocytoma (▶ Chap. 37).

Should a genetic background be looked for?

According to novel findings, at least 40% of sporadic pheochromocytomas/paragangliomas occur due to germ-line mutations of a limited set of genes inherited as autosomal dominant traits (▶ Chap. 37 on pheochromocytoma). The prevalence of germ-line mutations in paragangliomas is higher than in adrenal pheochromocytomas. Mutations of certain genes are linked to familial tumor

Table 38.1 Results of the first hormonal screen including urinary (24 h) catecholamines and serum chromogranin A

Analyte	Result	Normal range
Urinary metanephrines	294 µg/24 h	<375 µg/24 h
Urinary normetanephrines	10,507 µg/24 h	<780 µg/24 h
3-Methoxytyramine	989 µg/24 h	<425 µg/24 h
Chromogranin A	10,121.0 ng/mL	19.4–98.1 ng/mL

syndromes like multiple endocrine neoplasia type 2 (▶ Chap. 51), von Hippel-Lindau syndrome (▶ Chap. 52), neurofibromatosis type 1, and familial paraganglioma syndromes. (Mutations of several other genes have also been established to confer susceptibility to pheochromocytomas/paragangliomas.) Familial paraganglioma syndromes are the most important, as these predispose patients to extraadrenal pheochromocytomas. Familial paraganglioma syndromes are caused by mutations of genes coding for components of the mitochondrial succinate dehydrogenase (SDH) complex. The mutation screening in our patient did not show any mutations in the tested genes including succinate dehydrogenase B subunit (SDHB).

Are there clinical differences between the different familial paraganglioma syndromes?

Familial paraganglioma syndrome type 1 (PGL-1) is the most common form that is caused by mutations of the succinate dehydrogenase D subunit (SDHD) gene. Parasympathetic paragangliomas predominantly develop in the head and neck region (e.g., skull base and tympanic locations), and adrenal pheochromocytomas are more infrequent. Although all familial paraganglioma syndromes are inherited as autosomal dominant traits, the inheritance pattern of PGL-1 is unique as the disease can only be inherited from the father, irrespective of that whether the father is affected or only a carrier (maternal imprinting) (▶ Chap. 37).

Mutations of the SDHB gene are associated with metastatic paragangliomas in about 30% of patients (familial paraganglioma syndrome type 4 [PGL-4]). In PGL-4, sympathetic paragangliomas are usually found in the abdominal, pelvic, and thoracic cavities. The metastatic potential of PGL-4 makes it the paraganglioma syndrome with the worst prognosis. SDHB mutations were associated with renal cancer as well.

In both PGL-1 and PGL-4, adrenal pheochromocytoma is observed in about 25% of cases, but these secrete predominantly noradrenaline, and thus, typical pheochromocytoma symptoms are usually absent.

Three further familial paraganglioma syndromes are known that are associated with mutations in genes coding for components or associated proteins of the SDH complex (PGL-2: SDHAF2 [SDH complex assembly factor 2], PGL-3: succinate dehydrogenase C subunit (SDHC), PGL-5: succinate dehydrogenase A subunit (SDHA)) that are very rare, and their clinical characteristics are not as well defined as for PGL-1 and PGL-4.

What kind of imaging should be performed?

Chest-CT and abdominal-pelvic multiphasic CT or MRI scans are recommended after successful resection of the primary as a part of follow-up procedures. If a metastatic tumor is suspected, functional imaging, ^{123}I-MIBG (metaiodobenzylguanidine) scan or somatostatin receptor- based imaging (somatostatin receptor scintigraphy or ^{68}Ga-DOTATATE PET-CT) should be performed. ^{18}FDG (18-fluorodeoxyglucose) PET-CT and bone scan could also be useful.

What is MIBG (metaiodobenzylguanidine)?

MIBG is an analogue of noradrenaline that is taken up by chromaffin cells. Several drugs interfere with its uptake, such as phenothiazine, tricyclic antidepressants, antihistamines, opioid analgesics, tramadol, and calcium channel blockers, which should usually be stopped 24–72 h before the scan. Somatostatin-based functional imaging has better sensitivity for paragangliomas than MIBG.

What kind of treatment options are available for metastatic pheochromocytoma/paraganglioma?

Surgery can be performed even in metastatic cases to reduce tumor burden (debulking surgery), and thereby hormonal symptoms and improve the success of other treatment options. Other ablative treatments (e.g., chemoembolization, radiofrequency ablation) can also be tried. Systemic treatment options include radionuclide treatments and chemotherapy. ^{131}I-MIBG (metaiodobenzylguanidine) that is used with another isotope (^{123}I) in the imaging of pheochromocytomas can be used as a form of endoradiotherapy in metastatic tumors as it accumulates in chromaffin tissues. As pheochromocytomas/paragangliomas belong to the group of neuroendocrine tumors expressing high levels of receptors for somatostatin, radiolabeled somatostatin analogs can also be used (peptide receptor radionuclide therapy [PRRT], see ▶ Chap. 44 on carcinoid syndrome and intestinal neuroendocrine tumor for more detail). The most commonly used forms of systemic chemotherapy are the CVD protocol (cyclophosphamide-vincristine-dacarbazine) and the alkylating agent temozolomide. Sunitinib as a tyrosine kinase inhibitor is also being investigated in metastatic pheochromocytoma/paraganglioma.

In malignant adrenal pheochromocytomas associated with severe hypertension, the catecholamine analogue alpha-methyl paratyrosine can be tried, as it inhibits catecholamine production (▶ Chap. 37).

Follow-Up of the Case

Our Tumor Board proposed first the resection of the recurrent retroperitoneal tumor and then ^{131}I-MIBG treatment. The retroperitoneal tumor could be removed in toto, and the patient received 3700 MBq ^{131}I-MIBG. Two months later, his CgA level dropped to 371 ng/mL (normal <98.1 ng/mL), and the urinary normetanephrine and 3-methoxytyramine returned to the normal range. Lung metastases regressed.

One year later, both CgA and urinary metanephrine and 3-methoxytiramine levels increased again (CgA: 996.5 ng/mL, urinary 3-methoxytyramine: 696 μg/24 h, urinary normetanephrine: 4795 μg/24 h). Restaging CT showed an increase in size of the lung nodules, and lymph node metastases appeared at the resected primary. Despite progression, the patient had no complaints. A repeated radiotherapy with ^{131}I-MIBG was performed (3700 MBq again), and 2 months later CgA was mildly reduced, but both urinary normetanephrine and 3-methoxytyramine were higher than ever before (CgA: 793.5 ng/mL, urinary 3-methoxytyramine: 1338 μg/24 h, urinary normetanephrine: 9228 μg/24 h). Figure 38.1 shows an ^{123}I MIBG-SPECT-CT scan preceding the second treatments.

Systemic chemotherapy with CVD was started, but after six cycles, further progression was seen. Then, our Tumor Board decided for a somatostatin peptide radionuclide treatment, and the patient received ^{177}Lu-DOTATATE three times (3 × 7.4 GBq). (Figure 38.2 shows a SPECT-CT figure performed after the first ^{177}Lu-DOTATATE administration.) Unfortunately, further progression was noted, and therefore, a capecitabine-temozolomide combination was started based on recent literature data and the NCCN (National Comprehensive Cancer Network) guideline (▶ https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf).

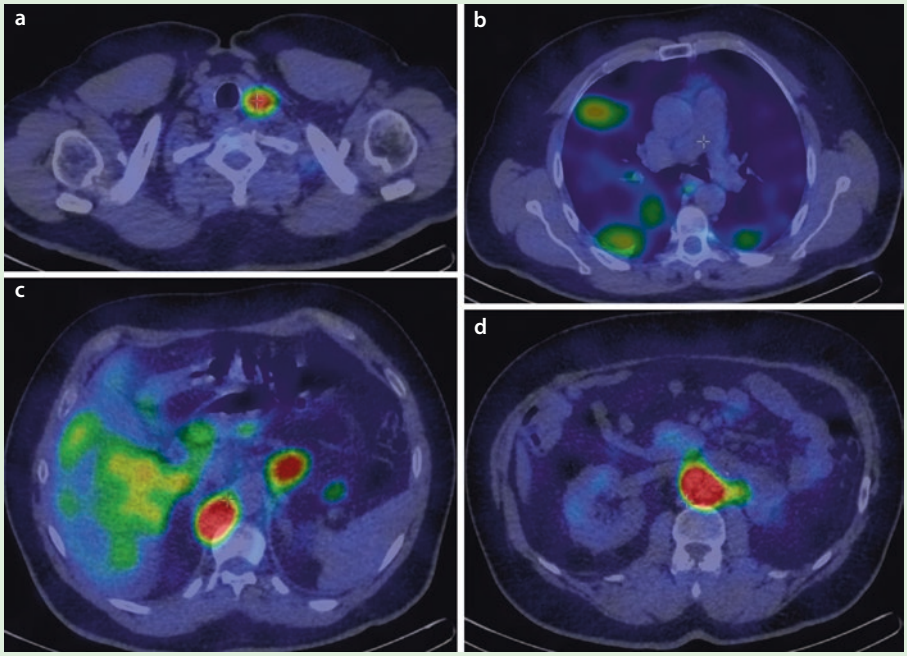

Fig. 38.1 ^{123}I-MIBG SPECT-CT scan of the patient before the second ^{131}I-MIBG treatment (axial images). Intensive ^{123}I-MIBG uptake in **a** cervical lymph node, **b** lung metastases, and **c**, **d** retroperitoneal lymph nodes

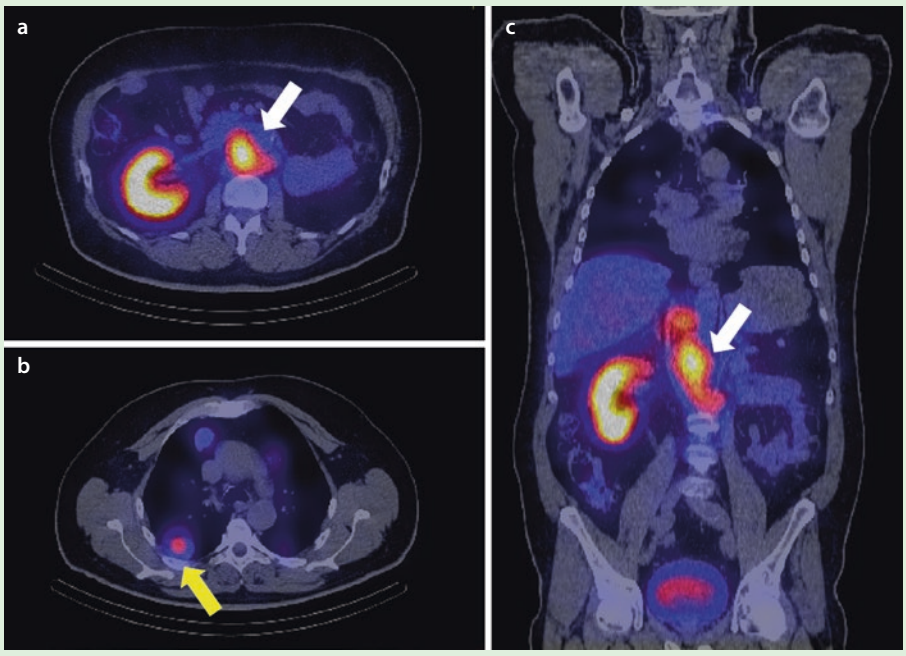

Fig. 38.2 SPECT-CT taken after the first ^{177}Lu-DOTATATE somatostatin peptide radionuclide treatment. **a** Retroperitoneal lymph node metastases in front of the spine (sagittal section) (white arrow), **b** metastasis in the lung (yellow arrow), **c** coronal section showing the retroperitoneal lymph node metastases (white arrow). (The kidney and urinary bladder are normally positive)

Tips

The reader is advised to read the previous chapter on pheochromocytoma (▶ Chap. 37) before beginning with this chapter. More details on peptide receptor radionuclide therapy can be found in the chapter on carcinoid syndrome and small intestinal neuroendocrine tumor (▶ Chap. 44).

Take Home Messages

- The term paraganglioma refers to an extraadrenal chromaffin tumor (pheochromocytoma).
- Paragangliomas are usually not associated with severe hypertension, as they secrete mostly norepinephrine.
- At least 40% of paragangliomas are associated with hereditary tumor syndromes caused by germ-line mutations. Mutations linked to genes coding for proteins involved or associated to the succinate dehydrogenase (SDH) complex are most prevalent in paragangliomas.
- A complex treatment involving surgery, ablative treatment, radionuclides (^{131}I-MIBG and somatostatin peptide radionuclide therapy), and systemic chemotherapy can be tried.

Suggested Reading

1. Agrawal A, Rangarajan V, Shah S, Puranik A, Purandare N. MIBG (metaiodobenzylguanidine) theranostics in pediatric and adult malignancies. Br J Radiol. 2018;91(1091):20180103. https://doi.org/10.1259/bjr.20180103.
2. Antonio K, Valdez MMN, Mercado-Asis L, Taieb D, Pacak K. Pheochromocytoma/paraganglioma: recent updates in genetics, biochemistry, immunohistochemistry, metabolomics, imaging and therapeutic options. Gland Surg. 2020;9(1):105–23. https://doi.org/10.21037/gs.2019.10.25.
3. Canu L, Pradella S, Rapizzi E, Fucci R, Valeri A, Briganti V, Giache V, Parenti G, Ercolino T, Mannelli M. Sunitinib in the therapy of malignant paragangliomas: report on the efficacy in a SDHB mutation carrier and review of the literature. Arch Endocrinol Metab. 2017;61(1):90–7. https://doi.org/10.1590/2359-3997000000217.
4. Corssmit EPM, Snel M, Kapiteijn E. Malignant pheochromocytoma and paraganglioma: management options. Curr Opin Oncol. 2020;32(1):20–6. https://doi.org/10.1097/cco.0000000000000589.
5. Eisenhofer G, Peitzsch M. Laboratory evaluation of pheochromocytoma and paraganglioma. Clin Chem. 2014;60(12):1486–99. https://doi.org/10.1373/clinchem.2014.224832.
6. Gimenez-Roqueplo AP. Adrenal tumors: when to search for a germline abnormality? Curr Opin Oncol. 2019;31(3):230–5. https://doi.org/10.1097/cco.0000000000000525.
7. Gupta G, Pacak K. Precision medicine: an update on genotype/biochemical phenotype relationships in pheochromocytoma/paraganglioma patients. Endocrine. 2017;23(6):690–704. https://doi.org/10.4158/ep161718.Ra.
8. Jimenez C, Erwin W, Chasen B. Targeted radionuclide therapy for patients with metastatic pheochromocytoma and paraganglioma: from low-specific-activity to high-specific-activity iodine-131 metaiodobenzylguanidine. Cancer. 2019;11(7) https://doi.org/10.3390/cancers11071018.
9. Nozieres C, Walter T, Joly MO, Giraud S, Scoazec JY, Borson-Chazot F, Simon C, Riou JP, Lombard-Bohas C. A SDHB malignant paraganglioma with dramatic response to temozolomide-capecitabine. Eur J Endocrinol. 2012;166(6):1107–11. https://doi.org/10.1530/eje-11-1098.
10. Sarkadi B. Patocs A (2019) hereditary diseases predisposing to pheochromocytoma (VHL, NF-1, paraganglioma syndromes, and novel genes). Exp Suppl. 2012;111:129–47. https://doi.org/10.1007/978-3-030-25905-1_8.
11. Schreiner F, Beuschlein F. Disease monitoring of patients with pheochromocytoma or paraganglioma by biomarkers and imaging studies. Best Pract Res Clin Endocrinol Metab. 2019;34:101347. https://doi.org/10.1016/j.beem.2019.101347.
12. Tong A, Li M, Cui Y, Ma X, Wang H, Li Y. Temozolomide is a potential therapeutic tool for patients with metastatic pheochromocytoma/paraganglioma-case report and review of the literature. Front Endocrinol. 2020;11:61. https://doi.org/10.3389/fendo.2020.00061.

Diseases of the Gonads

The fifth part of the book presents diseases of both male and female gonads. Polycystic ovary syndrome, the most common cause for anovulation and menstrual irregularities is discussed in ► Chap. 39. In the next chapter, Turner syndrome, a chromosomal abnormality that is the most common cause of primary amenorrhea is presented (► Chap. 40). The differential diagnosis and treatment of primary ovarian insufficiency is the focus of ► Chap. 41. The most common sex chromosome abnormality resulting in primary hypogonadism in men, Klinefelter syndrome, is presented in ► Chap. 42. An example for the disorders of sex differentiation, the rare complete androgen insensitivity that leads to a female phenotype in an individual with male karyotype and testes due to androgen receptor mutations is discussed in ► Chap. 43.

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Polycystic Ovary Syndrome

Carmen E. Georgescu

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P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_39

Opening

About 55–91% of anovulation cases harbor the polycystic ovary syndrome (PCOS), which represents the most frequent cause of androgen excess (AE) and the commonest endocrinopathy in women of reproductive age. This chapter discusses the symptoms, diagnostic criteria, and treatment options in PCOS.

Definition of the Disease

PCOS is a heterogeneous and dynamic disorder that clusters signs and symptoms of AE and chronic ovarian dysfunction. The etiology of the disease remains to be elucidated. Evidence suggests that PCOS is a polygenic disorder with contributive intrinsic (defect in steroidogenesis), environmental (bisphenol A, environmental toxins), or epigenetic factors leading to excessive androgen production and oligo/anovulation. Insulin resistance and compensatory hyperinsulinism further aggravate AE through theca cell hyperplasia and additionally by modulating gonadotropin secretion and stimulating adrenal androgen synthesis. In PCOS, AE promotes obesity and visceral adipose tissue dysfunction, thus creating a vicious circle and leading to metabolic dysfunction with dyslipidemia, type 2 diabetes mellitus (T2D), and subclinical vascular disease. These patients also feature subfertility, endometrial hyperplasia and increased risk of endometrial cancer, and psychological disorders (anxiety and depression).

In unspecified populations of women, the disease has a 4–16% prevalence rate.

Case Presentation

A 15.5-year-old girl was referred from dermatology for acanthosis nigricans (AN) around the neck, axillae, and the dorsal aspect of interphalangeal joints (Fig. 39.1a, b) and oligomenorrhea (menses every 45–60 days) to our consultation in endocrinology. The age at menarche was 11.6 years, and over the past 2 years she gained 12 kg and developed moderate acne. On physical examination, the girl was obese (body mass index 28.5 kg/m^2, >95th percentile) and had a waist

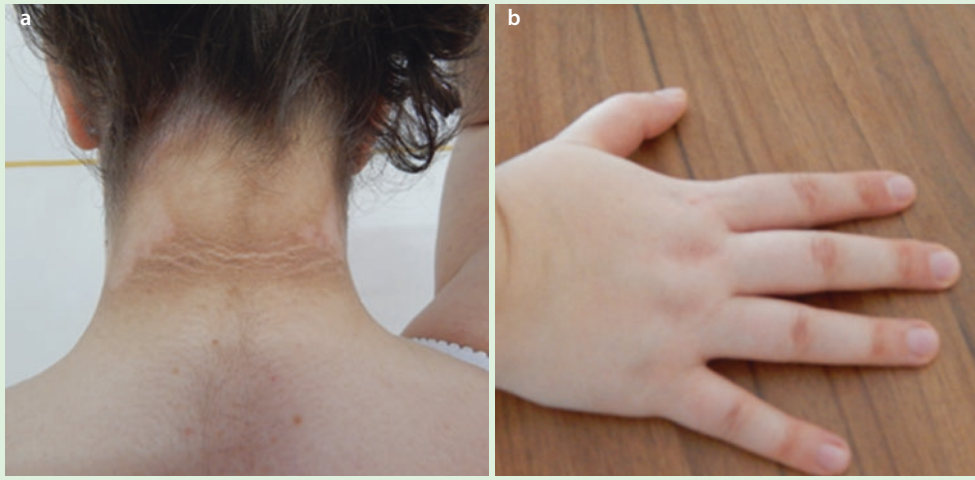

Fig. 39.1 Acanthosis nigricans in the neck **a** and interphalangeal joints **b** in an adolescent girl

circumference of 84 cm, normal blood pressure (70th percentile), and a Ferriman–Gallwey score of 12. Electro-chemiluminescence immunoassay androgen assessment in the morning showed the following results: total testosterone (TT) 2.75 (0.24–2.6) nmol/L, sex-hormone binding globulin (SHBG) 19.9 (18–114) nmol/L, and 17-hydroxyprogesterone (17–OHP) 3.75 nmol/L (124 ng/dL, normal). Dehydroepiandrosterone sulfate (DHEAS) 8.9 μmol/L (2.44–9.77) and androstenedione 7.67 (0.05–4.67 ng/mL) were also assessed. Pelvic ultrasound showed an ovarian volume of 8.5 cm^3 with polycystic appearance.

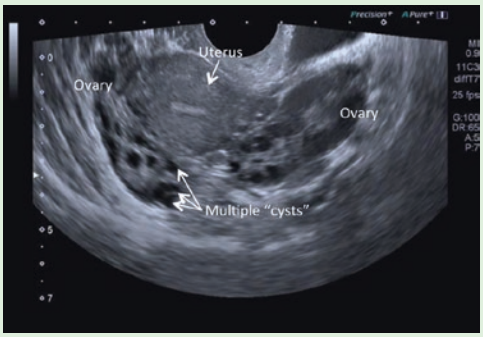

Fig. 39.2 Polycystic ovary morphology on transvaginal ultrasound

What are the symptoms of androgen excess (AE)?

Signs and symptoms of AE include hirsutism, acne and seborrhea, male pattern alopecia, and, rarely, the virilization syndrome (muscle hypertrophy, deepening of the voice, breast atrophy, amenorrhea, and clitoromegaly).

What is the definition of hirsutism?

Hirsutism is excessive terminal hair that appears in a male pattern in women (hair growth in androgen-dependent areas of the body, for example, face, chest, back, belly, and thighs). Diagnosis of hirsutism is based on the Ferriman–Gallwey score above the 95th percentile for the population: for example, ≥8 in white and UK or US black women and ≥9–10 in Mediterranean, Hispanic, and Middle Eastern women. All cases of hirsutism need biochemical evaluation.

What are the diagnostic criteria of PCOS?

Sets of criteria have been developed for the diagnosis of PCOS. Whilst AE is a mandatory event of both National Institute of Health (NIH) and Androgen Excess and PCOS Society (AE-PCOS) definitions, the European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) Rotterdam consensus broadened the diagnosis of PCOS, requiring two of three features: oligo/anovulation, clinical and/or biochemical AE, and polycystic ovarian morphology (PCOM) determined mostly by ultrasound (optimally transvaginal) (Fig. 39.2), with the exclusion of etiologies mimicking the syndrome. More recently, diagnostic criteria in adolescents have been issued (Table 39.1).

How to interpret the androgen hormone profile in the patient?

The gold standard in androgen assessment is gas-chromatography (GC)–mass spectrometry (MS)- or liquid-chromatography (LC)–MS-based, which provides high accuracy; however, it is not routinely performed. Alternatively, measurement by automated or extraction chromatography immunoassay is reasonable in clinical practice. The elevated total testosterone (TT) in this patient is illustrative. In the symptomatic patient with a normal TT, assessment of sex-hormone binding globulin (SHBG) is mandatory, and free T (FT) should be expressed as calculated FT based on Vermeulen's formula (5th–95th percentiles limits established in an age- and BMI (body mass index)-matched population of women free of PCOS), correlating well with equilibrium dialysis LC-MS/MS

Table 39.1 Diagnosis criteria in adult, adolescent, and postmenopausal women with PCOS

Diagnosis system	Diagnosis criteria	Definition constraints
Adult women		
NIH (1990)	(i) Clinical and/or biochemical hyperandrogenism AND (ii) Oligo-anovulation	Androgen excess is mandatory in the anovulatory patient
ESHRE/ASRM (2003)	(i) Clinical and/or biochemical hyperandrogenism (ii) Ovulatory dysfunction (iii) PCOM	Two of three criteria are accepted for diagnosis
AE-PCOS (2006)	(i) Clinical and/or biochemical hyperandrogenism AND (ii) Ovarian dysfunction, i.e., ovulatory dysfunction and/or PCOM	Androgen excess is mandatory in a patient with either chronic ovulatory dysfunction and/or presence of PCOM
NIH 2012	ESHRE/ASRM 2003 criteria are reinforced WITH the specification of the disease phenotype	
Adolescent girls		
ESHRE/ASRM (2012)	(i) Clinical and/or biochemical hyperandrogenism AND (ii) Oligo-anovulation AND (iii) Ovarian volume > 10 cm^3	
ES (2013)	(i) Clinical and/or biochemical hyperandrogenism AND (ii) Persistent oligo-/anovulation, i.e., oligo-/amenorrhea or primary amenorrhea by age 16	Girls at least 2 years post-menarche Pelvic ultrasound is not diagnostic
AAP (2016)	(i) Abnormal uterine bleeding pattern, i.e., abnormal for age/gynecologic age for 1-2 years AND (ii) Evidence of hyperandrogenism	Pelvic ultrasound is not diagnostic Persistent TT elevation above adult norms corresponds best to hyperandrogenemia
ESPE (2017)	(i) Irregular menses/oligomenorrhea AND (ii) Clinical and/or biochemical hyperandrogenism	Girls at least 2 years post-menarche PCOM, severe cystic acne, obesity, and insulin resistance are not diagnostic
Postmenopausal women		
ES (2013)	(i) Clinical and/or biochemical hyperandrogenism AND (ii) Long-term history of oligo-amenorrhea	The diagnosis is retrospective

NIH National Institute of Health, *ESHRE/ASRM* European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine, *AE-PCOS* Androgen Excess and PCOS Society, *ES* Endocrine Society, *AAP* American Academy of Pediatrics, *ESPE* European Society of Pediatric Endocrinology

for serum FT even at SHBG <30 nmol/L. Hyperandrogenemic patients show lower SHBG due to suppression of liver expression by T and insulin resistance.

Is measurement of dehydroepiandrosterone sulfate (DHEAS) and androstenedione in AE useful?

Generally, high total or FT confirms hyperandrogenemia in clinical practice, but isolated DHEA excess (<600 µg/dL) has been demonstrated in 30% of adolescent girls and adults with PCOS. On top of that, 10% of women with PCOS may present with high androstenedione as the sole marker of biochemical AE. Several patients associate elevated levels of adrenal 11-oxygenated C19 androgens.

Is androstenedione related to the metabolic status of the patient?

High androstenedione predicts metabolic risk in PCOS. These patients are more prone to develop insulin resistance and dysglycemia, particularly in presence of both high T and androstenedione.

How relevant is PCOM in this case?

PCOM criteria may be met by up to 25% of ovulatory adult women (Fig. 39.2) and up to 50% of healthy adolescent girls (<8 years after menarche). Longitudinal evaluation of subjects with PCOM and regular menstrual status has confirmed that these are not at significant risk to develop PCOS. A mean ovarian volume >10 cm^3 (or single ovary >15 cm^3) should be considered as enlarged in adolescents (criteria not fulfilled by the patient). Hyperprolactinemia, hypothyroidism, and congenital adrenal hyperplasia (CAH) may exhibit an increased antral follicle count (AFC).

Is anti-müllerian hormone (AMH) a better predictor of PCOM status?

Serum AMH reflects secretion from early antral and larger follicles as these are in contact with the vascular bed. In PCOS, the number of growing follicles is increased and AMH appears to be more sensitive compared to the AFC to define follicle excess. Still, eumenorrheic patients with PCOS may have similar values to healthy women with PCOM. In adults, threshold values range between 10 and 57 pmol/L. An AMH >35 pmol/L has shown 92% sensitivity and 97% specificity to diagnose PCOS in presence of either oligo/anovulation or hyperandrogenism, as a surrogate of ultrasonography. Automated assays are available, and recently, an international standard for AMH has been subjected to evaluation. Prior to AMH use as diagnostic alternative to PCOM, further aspects need to be considered.

What are the challenges of PCOS diagnosis in the adolescent girl?

The criteria applied to define hyperandrogenemia during adolescence are confounded by developmental events. No clear T cutoff is validated. A follicular phase TT >42 ng/dL based on LC-MS/MS was suggested; for assays using an extraction step, TT >55 ng/dL or FT >9 pg/mL are likely consistent with hyperandrogenism. Normative data on the hirsutism score during early adolescence are lacking. Moderate–severe inflammatory acne vulgaris is an indicator to test for hyperandrogenemia. Distinguishing persistent oligomenorrhea from "physiological adolescent anovulation" is indicated by persistent (≥1–2 years) cycle length >45 days or dysfunctional uterine bleeding at 2 years post-menarche or primary amenorrhea in a girl with complete pubertal development. The AFC on ultrasound is not helpful in this group of age.

What are the clinical risk factors/conditions for PCOS?

Low birth weight (LBW) and premature pubarche (defined as development of pubic and axillary hair before the age of eight in girls) are linked to development of insulin resistance, hyperandrogenism, and dysovulation during adolescence, particularly in presence of visceral obesity. Early interven-

tion with metformin between ages 8 and 12 in girls with a history of LBW and/or premature pubarche who gain weight possibly disrupts the chain. There is concern that treatment with Gonadotropin-releasing hormone (GnRH) agonists in girls showing early puberty may increase the later risk of PCOS; however, clear evidence is lacking.

About 10% of women with functional hypothalamic amenorrhea (FHA) develop AE over time, particularly when they normalize their weight and, thus, progress to PCOS. About 50% of women fulfilling Rotterdam criteria of PCOS and presenting with anovulation and PCOM might have had FHA as underlying condition. Distinguishing between non-hyperandrogenic PCOS and FHA at some point might be difficult. The medical history and Luteinizing hormone (LH) secretory pattern (i.e., in FHA, typically Follicle-stimulating hormone (FSH) is normal or low-normal, but with low LH and FSH/LH ratio >1) in addition to preserved response to GnRH provides one clue.

How is the diagnosis of PCOS established in peri- and postmenopause?

Diagnosis of PCOS in peri-/postmenopausal women is retrospective upon a history of persistent oligomenorrhea and evidence-based hyperandrogenism, with exclusion of other causes of postmenopausal AE. We lack normative ranges of androgens during menopausal transition; generally, TT levels >1.38 nmol/L define postmenopausal hyperandrogenism. Transvaginal ultrasound PCOM supports the diagnosis but is inconstant and not used as a criteria for diagnosis.

Which other diseases exhibit PCOS-like features? (▶ Box 39.1)

Although a rare cause, in androgen-secreting tumors (AST), total and FT exceed the upper normal limit in all patients and will not respond to low-dose dexamethasone (DXM) suppression (test sensitivity 100% and specificity 88%). In women, a TT >5 nmol/L is indicative. Concomitant DHEAS levels above 600–700 µg/dL suggest adrenal origin of AST. Non-classic (late-onset) CAH shares many PCOS-like features, including PCOM, which was reported in 24–83% of CAH; an elevated early morning basal follicular phase 17-hydroxyprogesterone (17-OHP) plus Adrenocorticotropic hormone (ACTH)-stimulated 17-OHP >10 ng/mL point toward CAH. In symptomatic women with a positive family history or high-risk ethnic groups, 17-OHP needs to be measured even in presence of normal total or FT. Urinary or serum GC/MS- or LC/MS-steroid profiling is a specific tool in the diagnosis of enzymatic defects in patients with CAH; typically, patients with 21-hydroxylase deficiency will present high pregnanetriol, 17OHpregnanolone, and pregnanetriolone metabolites (▶ Chap. 34 on late-onset 21-hydroxylase deficiency).

Glucocorticoid resistance syndrome, caused by point mutations or deletions in the glucocorticoid receptor gene, mimics PCOS due to the combination of clinical hyperandrogenism and arterial hypertension, although some patients may be asymptomatic. Premature adrenarche may represent an early sign. Hypokalemia, elevated ACTH, and non-suppressible cortisol by low-dose DXM can be indicative (▶ Chap. 36).

Severe insulin resistant syndromes (SSIR) and PCOS-like features

In a clinical setting, exogenous insulin requirement of more than 3 units/kg body weight or fasting insulin levels above 20.9 µg/mL and/or peak insulin on Oral Glucose Tolerance Test (OGTT) above 209 µg/mL in non-diabetic, non-obese women with acanthosis nigricans (AN) and PCOS points toward SSIR. Familial partial lipodystrophy typically is associated with progressive loss of subcutaneous fat in the arms and legs, peri-pubertal face, neck and abdominal fat accumulation and eruptive xanthomas, plus metabolic abnormalities (hypertriglyceridemia, low high-density lipoprotein cholesterol [HDL-C] and non-alcoholic fatty liver disease [NAFLD]). Congenital general-

Box 39.1 Differential Diagnosis of Androgen Excess (AE) in Women

- Tumors
  - Androgen-secreting tumors (AST)
  - Adrenal AST
    - Adenoma
    - Adenocarcinoma
  - Ovarian AST
    - Sertoli cell tumors
    - Sertoli–Leydig cell tumors
    - Hilus cell tumors
    - Granulosa cell tumors
  - Pancreatic neuroendocrine tumor (pNET) releasing LH →PCOS
- Adrenal gland enzymatic defects
  - Congenital adrenal hyperplasia (CAH)
    - 21-hydroxylase deficiency
    - 11β-hydroxylase deficiency
    - 3β-hydroxysteroid dehydrogenase deficiency
    - 17α-hydroxylase/17,20-lyase deficiency
  - Apparent cortisone reductase deficiency
    - 11β-hydroxysteroid dehydrogenase type 1 deficiency[a]
  - Apparent DHEA sulfotransferase deficiency
    - PAPSS2 (3′-phospho-adenosine-5′-phosphosulfate) synthase 2 deficiency[a]
- Idiopathic hirsutism and hyperandrogenemia
  - Idiopathic hirsutism
    - Androgen receptor CAG repeat polymorphism[a]
  - Idiopathic hyperandrogenemia
- Drugs
  - Anabolic steroids (misuse, abuse), testosterone
  - Anticonvulsants (valproate acid, oxcarbazepine)
  - Anti-psychotic drugs (risperidone, olanzapine, aripiprazole, ziprasidone, quetiapine and phenothiazine)
  - Methyldopa, reserpine, metoclopramide, danazol
- Other endocrine and metabolic disorders
  - Hyperprolactinemia
  - Acromegaly
  - Thyroid disorders
  - Cushing's syndrome
  - Glucocorticoid resistance syndrome[a]
  - Severe insulin resistance syndromes
    - Generalized or partial lipodystrophy
    - Type A insulin resistance syndrome
    - Type B insulin resistance syndrome
    - Hyperthecosis of the ovary
    - Obesity
- Pregnancy-related hyperandrogenism[b]
  - Theca lutein cysts
  - Luteoma of pregnancy
  - P450 Aromatase deficiency in the fetus
  - P450 Oxidoreductase deficiency in the fetus

[a]May present as premature adrenarche or pubarche

[b]Associates transient maternal virilization

ized lipodystrophy is usually apparent from birth or early childhood, with almost complete absence of fat and PCOS-like features in women. Most affected genes in insulin post-receptor pathways include *LMNA, PPARG* (adipocyte differentiation), *CAV1, CAVIN1, AGPAT2* (fatty acid uptake and triglyceride [TG] synthesis) and *BSCL2, PLIN1* (lipid droplet formation) genes. In contrast, dyslipidemia is lacking in Type A (i.e., insulin receptor gene mutations) or Type B (i.e., insulin receptor autoantibodies) SSIR due to lack of hepatic insulin resistance, which is mediated by the insulin receptor.

Obesity-Induced PCOS

The variant of obesity-triggered PCOS is suggested by early body fat accumulation during adolescence, leading to augmented T production by the ovary and through adipocyte enzymatic conversion by Type 5 17β-hydroxysteroid-dehydrogenase. Obesity-

related hyperinsulinism has been shown to be responsible of enhanced androgen production rate in the theca cells. Overall, induction of PCOS by obesity per se is subjected to controversy.

What kinds of PCOS phenotypes are known?

Patients fulfilling classic NIH criteria, that is, phenotype A (hyperandrogenism and oligo/anovulation and PCOM) and phenotype B (hyperandrogenism and oligo/anovulation), have the highest degree of metabolic abnormalities and vascular risk, even after matching for BMI with controls. Prominent menstrual irregularities tend to normalize with aging. Hyperandrogenic-ovulatory women (i.e., phenotype C) are generally leaner and have milder metabolic abnormalities, mostly related to the presence of abdominal adiposity. Evaluation of intima-media thickness of the carotid artery shows less impaired values compared to classic phenotypes. Anovulatory, non-hyperandrogenic phenotype D most often shows normal insulin sensitivity and lipids, when matched for visceral adiposity with controls. Obesity may "convert" milder phenotypes into classic PCOS phenotype and aggravate both reproductive and metabolic consequences of AE. Rapid weight gain may precede development of PCOS (e.g., adolescence).

Is obesity a relevant feature for the diagnosis in this girl?

Obesity and metabolic abnormalities are commonly associated to PCOS, however not required for diagnosis of PCOS or identification of the phenotype.

What are the predictors of metabolic abnormalities in PCOS?

A high BMI, a history of gestational diabetes mellitus (GDM), and a familial history of T2D predict metabolic abnormalities in PCOS. In turn, first-degree relatives of women with PCOS including peri-pubertal daughters are at risk for dysglycemia and progression to T2D.

What kind of cardiovascular risk factors are associated with PCOS?

PCOS clusters a wide variety of cardiovascular risk factors including the atherogenic lipid profile (high VLDL [very low-density lipoprotein] number and TG (triglycerides), low HDL-C and reduced LDL-C [low-density lipoprotein] particle size). High VLDL and a more atherogenic small dense LDL-C predominance persist even after matching for BMI and insulin resistance. All patients with PCOS should receive a lipid test, with LDL-C set as primary therapeutic target. A 2-hour OGTT should be done as screening in all or at least in patients at risk (BMI $\geq$30 kg/m^2 or BMI <30 kg/m^2 but age >40 years or familial history of T2D or history of GDM). Alternatively, HbA1c may be considered.

Women with PCOS are at four-fold higher risk to develop NAFLD in comparison to healthy women. The pathogenesis of NAFLD is complex, with genetics, insulin resistance, obesity, diet, and environmental factors including bisphenol A as the most important contributors. Screening for fatty liver is not recommended; however, in phenotypes at risk, routine evaluation is warranted.

PCOS is associated with a prothrombotic state. Overweight and obese premenopausal PCOS feature early-onset arterial hypertension, higher prevalence of coronary artery calcifications, and, apparently, increased left ventricular mass. Less clear data are reported in lean and non-insulin resistant phenotypes. Despite the indisputable higher cardiovascular risk profile at young age, incidence of cardiovascular morbidity and mortality in women with PCOS is not yet clarified and could be limited to the classic phenotype. PCOS traits fade with age, and menopausal transition in non-PCOS shows similar metabolic and endocrine changes to PCOS, with reduced

hyperandrogenemic gradient and "catch-up" effect in cardio-metabolic risk.

What was the result of metabolic evaluation in this adolescent patient?

Basal hyperinsulinemia 26.2 (2.6–24.9) μU/mL, hypertriglyceridemia 150 (<150) mg/dL, HDL-C 43 (>40) mg/dL, and fasting glucose 90 (<100) mg/dL were found in the patient, not fulfilling International Diabetes Federation (IDF) 2009 criteria for metabolic syndrome (MetS). No abnormalities were detected in OGTT, to be repeated in 2 years.

Is there a risk related to pregnancy and PCOS?

These women have around three-fold higher risk to develop GDM, hypertension, and preeclampsia in addition to three-fold increased perinatal mortality of the neonate. Metformin (2 g/day) improves pregnancy outcome in patients with GDM or T2D, by inhibition of the mechanistic/mammalian target of rapamycin (mTOR) pathway with reduction of hyperinsulinemia and inflammation and prevention of fetal macrosomia. However, prevention of GDM by metformin as well as an impact on pregnancy outcomes in pregnant non-diabetic PCOS remains controversial.

Follow-up of the Patient's Case

Diet, physical exercising, and a 30-μg ethinylestradiol (EE2)/levonorgestrel contraceptive were initiated in this patient exhibiting hyperandrogenism.

What kinds of treatment regimens are available in hyperandrogenic phenotypes?

Combined oral contraceptives (COC)

Low-dose (20–35 μg EE2) oral contraceptives are first-line option in adolescents and adult women with AE and menstrual irregularities not desiring pregnancy. A less than 30 μg daily EE2 dose potentially affects peak bone mass in adolescents. The more severe the AE symptoms (hirsutism and acne) are, the more obvious the benefits due to suppression of ovarian androgen production. A 50–70% endometrial cancer risk reduction with prolonged use is expected. PCOS increases 1.55-fold arterial and two- to three-fold venous thromboembolism (VTE), respectively, compared with non-PCOS subjects. The VTE risk appears to be alleviated in COC users due to decrease in androgens. Ideally, therapy is started with a levonorgestrel-based COC (low-risk VTE progestin). On long term, switching to a third- to fourth-generation progestin compound (i.e., desogestrel, gestodene, drospirenone, or cyproterone acetate [CPA]) might be considered. Progestin monotherapy is an alternative in women at risk for thrombotic disease; however, irregular bleeding may persist and hyperandrogenism is not well controlled.

Antiandrogens

Commonly used antiandrogens include cyproterone acetate (CPA) and spironolactone, usually in combination to a COC to allow sequential administration (e.g., 10–15 days/cycle for CPA) and avoid menstrual irregularities and disorders of sex development in the offspring in this sexually active population (spironolactone). Flutamide, a non-steroidal androgen receptor blocker, and finasteride, a 5α-reductase inhibitor, have been used in both adolescents and adult women. Low-dose flutamide (62.5–250 mg/day), combined with COC, improves hirsutism and acne in addition to insulin sensitivity and lipid profile in adolescent PCOS, although hepatotoxicity is not excluded (Table 39.2).

Hirsutism: Topical Therapy

Direct hair removal is targeted toward residual hair excess, and permanent methods are widely available (Table 39.2).

How to tackle metabolic abnormalities in PCOS?

Table 39.2 Treatment of PCOS

Drug	Adult women Adolescent girls	Potential adverse effects
Systemic drugs		
Oral contraceptives	20–35 μg/day EE2 + progestin 21 out of 28 days/month	Headache, breast tenderness, TG elevation, increased risk of venous thromboembolism, increased risk of insulin resistance (BMI ≥ 38 kg/m^2), decreased libido Potential impairment of bone mineral density (BMD) with ultra-low-dose COC (20 μg) in adolescents
Cyproterone acetate	25–100 mg/day	Nausea, liver toxicity, irregular menses, pseudo hermaphroditism of the male fetus, decreased libido
Spironolactone	100–200 mg/day 50–200 mg/day	Irregular menses, headache, hypotension, disorders of sex development of the male fetus, decreased libido
Flutamide	250–500 mg/day 62.5–250 mg/day	Liver toxicity, pseudo hermaphroditism of the male fetus
Finasteride	2.5–5 mg/day 1–5 mg/day	Disorders of sex development of the male fetus, liver toxicity (rare)
Metformin	1–3 g/day 0.5–1 g/day	Gastrointestinal (cramps, bloating, nausea, vomiting), usually mild when dose increases progressively and transient Lactic acidosis[a]
Liraglutide	1.2–1.8 mg/day or 3 mg/day –	Gastrointestinal (nausea) Contraindication: pregnancy, history of pancreatitis, C-cell thyroid carcinoma, or at risk
Orlistat	120 mg t.i.d. with meals –	Steatorrhea, fat-soluble vitamins deficiency (vitamins A, D, E, K supplements and β-carotene should be given)
Pioglitazone	15–30 mg/day 7.5–30 mg/day	Weight gain
Myo-inositol	4 g/day –	
Topical treatments (hirsutism)		
Electrolysis		Pain (topical anesthetic cream is useful) Indication: white or blonde hair
Photo epilation (IPL or laser)		Indication: brown, black, or auburn hair Pain, paradoxical hair growth (PH) after laser epilation (women with darkly pigmented skin are at high risk), perifollicular inflammation, hyper/hypopigmentation, scarring (very rare, in women with darkly pigmented skin), eye injury
Eflornithine 15%	Twice daily	Local effects: burning, itching, dry skin In combination, it speeds up the effect of photo epilation

EE2 ethinylestradiol, *IPL* intense pulsed light
[a]Rare, in patients at risk

- Weight loss is the mainstay of first-line treatment in overweight/obese PCOS, and a reduction as little as 5% from initial body weight improves reproductive outcomes. Quality of diet has independent effects particularly advanced glycosylation endproducts (AGE)-rich food should be avoided as via AGE-receptor (RAGE) these promote both insulin resistance and abnormal follicular growth with anovulation.

- *Metformin*

- Metformin improves insulin sensitivity in both obese and non-obese insulin resistant patients and decreases low-grade chronic inflammation, endothelial dysfunction, and thrombogenic potential. Fasting hyperinsulinemia predicts more profound improvement of insulin and lipid profile under metformin. Other studies suggest approximately ≈20 mg/kgbw as efficient dosage. Metformin may lower androgens (T, androstenedione) and as second-line indication efficiently tackles menstrual irregularities and anovulation in women who cannot take or tolerate COC. However, its effect on hirsutism is weak, and metformin should not be used as first-line treatment of skin manifestations in PCOS.

- *Glucagon-Like Peptide (GLP)-1 Analogues*

- Incretin mimetics liraglutide and exenatide represent a therapeutic option in women with PCOS and T2D. Low-dose liraglutide as monotherapy or in combination to metformin promotes weight loss and reduction in waist circumference and T levels in overweight/obese non-diabetic PCOS in addition to improving endothelial dysfunction and decreasing fat liver content. It appears that liraglutide has superior effects compared to metformin in promoting weight loss in PCOS and additive effects of the low-dose liraglutide–metformin combination can be expected. High-dose liraglutide (3 mg/d), lately approved for obesity management, should be considered in PCOS with a BMI >30 kg/m^2 or >27 kg/m^2 and diabetes or high blood pressure. GLP-1 analogues should not be prescribed to pregnant women or patients at risk for C-cell thyroid carcinoma or with a history of pancreatitis.

- *Orlistat*

- The gastric and pancreatic lipase inhibitor Orlistat induces modest weight loss and exerts similar effects on androgens when compared to metformin. Improvement in lipid profile, particularly TG and LDL-C, has subsequent favorable effects on insulin resistance. The drug may interfere with absorption of fat-soluble vitamins (A, D, E, K) and supplements are recommended at bedtime. Absorption of COC is not affected; however, if severe diarrhea occurs, contraceptive ability might be impaired.

- *Myo-Inositol and D-Chiro-Inositol*

- Inositols are inositol triphosphate (IP3) precursors involved in insulin signal transduction. Myo-inositol lowers fasting insulin and insulin resistance indices to a similar extent to metformin and improves LDL-C in PCOS, and has a good tolerance profile. At the ovarian level, myo-inositol ameliorates FSH signaling; therefore, oocyte and possibly embryo quality and maturation are improved. The 40:1 combination of myo- and D-chiroinositol appears to lower hyperinsulinism and lipids, in addition to potentially restoring ovulation.

- *Metabolic Surgery*

- About 15% of the subjects undergoing diet and weight loss intervention are able to maintain their reduced weight. Several guidelines advocate for use of bariatric surgery as second-line medical procedure in obese PCOS (>30 kg/m^2) with diabetes. In patients with a BMI > 50 kg/m^2, surgery may represent an efficient first-line option in treating metabolic dysfunction.

- *Statins*

- Women with PCOS that meet the criteria may benefit from statin therapy; however, apart from decreasing total and LDL-C and fat liver content, no effect on insulin resistance is expected. Statins do not impact anovulation and exert only minor influence on androgens.

- *Other Drugs*

- *Naltrexone* reduces body weight and to some extent androgen levels. No data are available, however, on the use of naltrexone-bupropion in PCOS. *Acarbose,* a reversible α-glucosidase inhibitor, lowers digestion of polysaccharides, thus delaying glucose absorption and improving lipids, but there is similarity to metformin with respect to other outcomes (i.e., ovulation rate, menstrual cyclicity), including gastrointestinal side effects. *Vitamin D* deficiency needs correction in patients with PCOS, as this will ameliorate glucose tolerance, dyslipidemia, and androgens, in spite of no causal interrelationship between PCOS status and vitamin D. *Thiazolidinediones* may represent a second-line option in insulin resistant PCOS, but are rarely given.

- **How do oral contraceptives and antiandrogens impact on the metabolic risk in PCOS?**

- Oral contraceptives might alter insulin sensitivity in both healthy women and PCOS; however, there is no evidence of increased risk of diabetes with the exception of severely obese PCOS patients (BMI >38 kg/m^2). They reduce visceral fat in overweight/obese PCOS. Thus, individual cardio-metabolic risk stratification is needed prior to COC prescription. Triglycerides may increase in some COC users. HDL-C may rise in obese women. Overall, COC therapy benefits outweigh risks in the majority of patients with PCOS. An improved lipid profile is expected with antiandrogens. Spironolactone lowers TG levels and may increase HDL-C. Likewise, flutamide therapy decreases total and LDL-C in addition to TG.

- *Combination Regimens*

- In PCOS, combination of drugs tracks multiple targets and allows adjustment of therapeutic doses to the individual tolerance. On the long term, achieved benefits might be superior to drug monotherapy. They are increasingly used in clinical practice (e.g., COC plus spironolactone or CPA, COC plus metformin, laser treatment plus eflornithine).

- **Is there a role for ovarian surgery in the management of PCOS?**

- For patients with PCOS, aromatase inhibitor letrozole should be considered as first-line therapy for induction of ovulation due to apparently higher live birth rate than with clomiphene citrate. (Clomiphene is a selective estrogen receptor modulator substance that induces GnRH, LH, and FSH by affecting estrogen receptors of the hypothalamus.) In women for whom letrozole or clomiphene citrate ± metformin fail to result in pregnancy, second-line intervention includes either gonadotropin stimulation or laparoscopic ovarian drilling with laser or diathermy. However, the effect of ovarian drilling as a primary therapy for patients with PCOS and subfertility remains to be evaluated.

Tips

The reader is advised to read the chapters on late-onset 21-hydroxylase deficiency (► Chap. 34), pituitary Cushing's disease (► Chap. 3), adrenal Cushing's syndrome (► Chap. 27), and glucocorticoid resistance (► Chap. 36).

Take Home Messages

- PCOS is the most frequent cause of androgen excess and anovulation in women and the most common endocrine abnormality in women of reproductive age.
- PCOS diagnosis criteria are related to the patient's developmental status.
- High total testosterone and/or free testosterone levels certify androgen excess; if normal, dehydroepiandrosterone sulfate or androstenedione may be indicative.
- Phenotype identification guides metabolic and cardiovascular risk and disease management.
- Oral contraceptives ± antiandrogens are the first-line options with benefits outweighing risks. Comprehensive assessment and follow-up is mandatory.
- In obese and/or insulin resistant patients, the focus is on weight loss (diet, lifestyle). Adjuvant drugs may improve metabolic, endocrine, and reproductive outcome in selected cases.

Suggested Reading

1. ACOG Committee on Practice Bulletins – Gynecology. Polycystic ovary syndrome. Pract Bull. 2018;194:e157–71.
2. Conway G, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Franks S, Gambineri A, et al. The polycystic ovary syndrome: a position statement from the European Society of Endocrinology. Eur J Endocrinol. 2014;171(4):P1–29. https://doi.org/10.1530/EJE-14-0253.
3. Georgescu CE. Polycystic ovary syndrome and cardio-metabolic abnormalities: how to manage? Acta Endocrinol (Buchar) XI. 2015;(1):77–83. https://doi.org/10.4183/aeb.2015.77.
4. Ibanez L, Oberfield SE, Witchel SF, Auchus RJ, Chang RJ, Codner E, et al. An international consortium update: pathophysiology, diagnosis, and treatment of polycystic ovarian syndrome in adolescence. Horm Res Paediatr. 2017;88(6):371–95. https://doi.org/10.1159/000479371.
5. Idkowiak J, Elhassan YS, Mannion P, Smith K, Webster R, Saraff V, et al. Causes, pattern and severity of androgen excess in 487 consecutively recruited pre- and post-pubertal children. Eur J Endocrinol. 2019;180(3):213–21. https://doi.org/10.1530/EJE-18-0854.
6. Ilie IR, Georgescu CE. Polycystic ovary syndrome-epigenetic mechanisms and aberrant MicroRNA. Adv Clin Chem. 2015;71:25–45. https://doi.org/10.1016/bs.acc.2015.06.001.
7. Martin KA, Anderson R, Chang RJ, Ehrmann DA, Lobo RA, Murad H, et al. Evaluation and treatment of hirsutism in premenopausal women: an Endocrine Society Clinical Practice guideline. J Clin Endocrinol Metab. 2018;103(4):1233–57. https://doi.org/10.1210/jc.2018-00241.
8. Pasquali R, Diamanti-Kandarakis E, Gambineri A. Secondary polycystic ovary syndrome: theoretical and practical aspects. Eur J Endocrinol. 2016;175(4):R157–69. https://doi.org/10.1530/EJE-16-0374.

Turner Syndrome

Judit Major and Peter Igaz

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_40

Opening

Turner syndrome is one of the common chromosomal abnormalities in humans that is the most frequent cause of primary/hypergonadotropic hypogonadism (amenorrhea) in women. It is a complex developmental abnormality involving ovarian dysgenesis, short stature, and cardiovascular abnormalities. In this chapter, we focus on the management of Turner syndrome in adult patients.

Definition of the Disease

Turner syndrome is caused by a complete or partial deficiency of one of the two X chromosomes in women. The typical karyotype is represented by X monosomy (45 X,0) in about 50% of patients when there is only one X chromosome instead of a pair, whereas the rest of the karyotypes include Xq-isochromosome (46, X, i (X)q), partial deletions of the X chromosome (short arm [Xp] or long arm [Xq]), and rarely ring chromosome. (Isochromosome means that a chromosome is composed of either two long or two short arms, and thus the distribution of chromosome arms is shifted to 3:1 [partial trisomy vs. monosomy] instead of the normal 2:2 regarding the normal two chromosomes in a cell.) The loss of the short arm (Xp) of the X chromosome is related to more typical symptoms of Turner syndrome. Mosaicism is also quite frequent, that is, the presence of different cell lines in the body (e.g., 45 X,0/46 X,X or 45 X,0/47/XXX). Whereas patients with pure monosomy are usually infertile, fertility can be preserved in some mosaic cases. Rare mosaic cases include fragments of the Y chromosome (in about 10% of cases), and these are important to identify as these are at an increased risk of gonadoblastoma development, and prophylactic gonadectomy is necessary in these cases.

The prevalence of Turner syndrome varies between 1:2000 and 1:2500 live births; however, its frequency is even higher in aborted fetal specimens, suggesting that many fetuses die in utero. Turner syndrome is the most frequent cause of primary amenorrhea defined as no menstrual cycle by the age of 15 years or thereafter in women and is associated with typical physical characteristics. Streak gonads are typical with no follicles. The clinical course of amenorrhea is however quite variable, as some patients with Turner syndrome initially have menstrual cycles, but then secondary amenorrhea develops. Some patients, especially with mosaicism, can have normal menstrual cycles (but even 2–3% of patients with pure X monosomy can have menstrual cycles), as well. Spontaneous breast development is observed in 21–50% of patients. Other major manifestations include cardiovascular abnormalities, autoimmune disorders, renal abnormalities, hearing loss, and osteoporosis.

Whereas formerly reduced intelligence quotient was suspected to be associated with Turner syndrome, novel studies have not confirmed this (except for Turner syndrome associated with ring X chromosome), but there can be some problems with non-verbal and visuospatial abilities.

Case Presentation

A 64-year-old lady was referred to our center because of dizziness related to iron deficiency microcytic anemia. She had short stature (154 cm). Her ring fingers appeared to be conspicuously short (Fig. 40.1a), and her fourth and fifth toes were also very short (Fig. 40.1c). X-ray of her hand revealed a short fourth metacarpal to be responsible for the short ring finger (Fig. 40.1b). Moreover, a Madelung deformity of the wrist was also seen, that is, the dorsal subluxation of the ulna head due to premature growth arrest along the medial volar

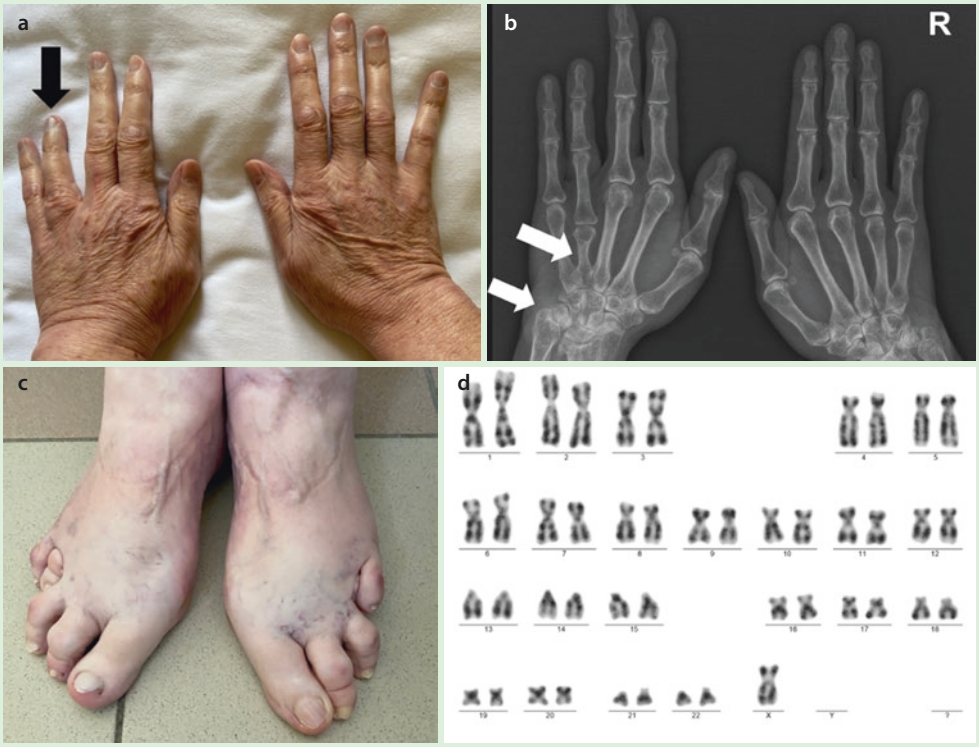

Fig. 40.1 **a** Photograph of the patient's hands shows the conspicuously shorter left fourth finger. **b** An x-ray of the patient's hands shows the short left fourth metacarpal and the Madelung deformity—subluxation of the distal end of the ulna (arrows). **c** The patient's feet with a short fourth toe. **d** Karyogram showing X-monosomy. (Reproduced with permission from Major J, Pusztai P, Igaz P. A short ring finger points to a diagnosis of Turner syndrome again. [Clinical Picture], *The Lancet*, 395, Pe51, 2020, ▶ https://doi.org/10.1016/S0140-6736(20)30235-X)

aspect of the distal radius (Fig. 40.1b). Her chest was shield like with nipples widely spaced (Fig. 40.2). Physical examination also revealed kyphoscoliosis, and X-ray revealed a compression fracture of the L2 (lumbar 2) vertebra. She told that she never had menstrual cycles, but did not know the cause, nor did she receive any therapy for that. She had hypertension and was taking L-thyroxine for hypothyroidism caused by Hashimoto's thyroiditis. In addition to these, she was also partially deaf.

Gastroduodenal erosions and a gastric ulcer were found in the background of her microcytic anemia that did not require blood transfusion.

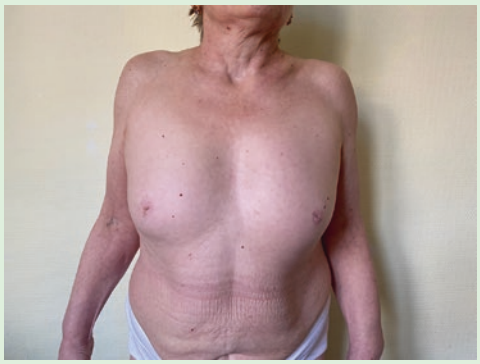

Fig. 40.2 Shield-like chest of the patient with widely spaced nipples

Which of these features make the diagnosis of Turner syndrome likely?

Short stature and primary amenorrhea (no menstrual cycles in the patient's history) are the main clues for suspecting Turner syndrome in this case. Regarding the other skeletal abnormalities, the short ring finger (in 30–40%), Madelung deformity (in 5%), shield-like chest (30%), and a short, webbed neck (40%) are also characteristic features. Webbed neck (pterygium colli) is a classical feature comprising a bilateral skin fold from the mastoid to the acromion.

The vertebral fracture was most probably related to osteoporosis that could be related to the lack of estrogen for many decades. Autoimmune diseases, including Hashimoto's thyroiditis, are common in Turner syndrome patients, and hearing loss is also typical.

Is there another endocrine disease that is also associated with a short ring finger?

Albright's hereditary osteodystrophy, which is a form of pseudohypoparathyroidism (type 1a), is also associated with a short fourth metacarpal. Pseudohypoparathyroidism is a resistance to the action of parathyroid hormone (PTH) due to mutations in genes coding proteins necessary for PTH signal transduction (pseudohypoparathyroidism type 1 is related to mutations in the *GNAS1* gene coding for a subunit of a guanosine triphosphate (GTP)-binding protein). Patients therefore display hypocalcemia, but serum PTH levels are high. Albright's hereditary osteodystrophy includes further phenotypic features such as short stature, round face, obesity, and developmental delay, but there is no gonadal involvement.

How should the diagnosis of Turner syndrome be confirmed?

The diagnosis is based on karyotype analysis. In children, growth failure and the characteristic phenotypic features along with heart defects represent indications for testing. In adolescents, amenorrhea and lack of the larche (breast development) can raise suspicion. Patients with sex chromosome parts (marker chromosome elements) on the standard karyogram and/or signs of virilization should be candidates for the analysis of Y-chromosome fragments (usually by FISH [fluorescence in situ hybridization]).

In our patient, karyotyping confirmed the classical 45X,0 karyogram showing X-monosomy (Fig. 40.1d). Actually, 2 weeks after her initial admission, her family brought documents showing that karyotyping was already performed 40 years earlier, and the diagnosis was established; however, she received no treatment in the meantime, and the diagnosis was thus forgotten.

What would the hormonal panel show?

Being a form of primary hypogonadism, estradiol (E2) is low, and pituitary gonadotropins (luteinizing hormone (LH) and follicle stimulating hormone (FSH)) are elevated. In our case, however, as the patient was already over 60 when referred to our department, no such panel was done, since the normal postmenopausal period would also show the same, and therefore, it would not bring any additional benefit.

Thyroid stimulating hormone (TSH) should be measured as Turner syndrome patients are at an increased risk for autoimmune thyroiditis (Hashimoto). Our patient already received levothyroxine substitution.

What kind of further investigations should be performed?

Table 40.1 summarizes the major clinical manifestations and complications of Turner syndrome.

Turner syndrome is associated with cardiovascular abnormalities in about 50% of patients. Cardiovascular abnormalities include aortic valve abnormalities (bicuspid aortic valve), aortic coarctation, aortic arch abnormalities, atrial and ventricular septum defects, persistent left superior vena cava, and pulmonary venous abnormalities. The risk of aortic dissection and

Table 40.1 Clinical features of Turner syndrome

Organ system	Manifestation
Skeletal	Short stature Webbed neck Shield-like chest Short ring finger Madelung deformity Cubitus valgus Kyphosis, scoliosis
Ovarian failure	Primary amenorrhea
Bones	Osteoporosis
Cardiovascular anomalies	Bicuspid aortic valve Aortic coarctation Aortic dissection Elongated aortic arch Ventricular and atrial septal defects Venous abnormalities (superior vena cava, pulmonary) Hypertension Heart conduction defects
Congenital renal malformations	Malformations of the collective system Malrotations Horseshoe kidney
Hearing abnormalities	Recurrent middle ear infections in children (conductive abnormalities) Progressive sensoneural hearing loss in adults Cholesteatoma
Ocular abnormalities	Nearsightedness, farsightedness, strabismus, amblyopia
Liver	Elevated liver enzymes (transaminases [alanine and aspartate aminotransferases] and gamma glutamyl transpeptidase)
Autoimmune abnormalities	Hashimoto's thyroiditis/ primary hypothyroidism Celiac disease Inflammatory bowel disease
Tumor	Gonadoblastoma associated with karyotypes including Y-chromosome fragments
Psychology	Impaired non-verbal skills

rupture is increased in Turner syndrome patients, which represents major causes for sudden death. Conduction abnormalities, for example, prolonged QT-interval, are observed in 20–40% of affected patients. About 30–50% of adult Turner syndrome patients have hypertension. Echocardiography and electrocardiogram should therefore be regularly performed in Turner syndrome patients.

Renal developmental abnormalities are seen in 30–40% of patients. These include malrotation, horseshoe kidney, and malformations of the collective system. There is an increased risk of pyelonephritis and urinary obstruction. Abdominal ultrasound can be used to reveal these abnormalities.

Due to the chronic lack of estrogen, the risk of osteoporosis is highly increased in Turner syndrome. Our patient already had a vertebral fracture.

Beside Hashimoto's thyroiditis and hypothyroidism (in up to 40% of adult cases), the risk for other autoimmune disorders including celiac disease (2–3%) and inflammatory bowel disease (3–4%) is also increased.

Eye and hearing abnormalities are also frequent in Turner syndrome patients. Hearing abnormalities are related to the increased likelihood of middle ear infections in children and cholesteatoma formation (conductive forms), but progressive sensoneural hearing loss is also observed in about 50% of adult patients.

Turner syndrome patients often display an elevation of liver enzymes that is mostly without clinical significance. Obesity and both type 1 and type 2 diabetes mellitus are more common in Turner syndrome than in the normal female population.

As discussed earlier, the presence of a chromosome Y fragment predisposes patients to gonadoblastoma formation, and therefore, in these cases, prophylactic gonadectomy is warranted.

Altogether, Turner syndrome is associated with serious morbidity, and patients have a three-fold higher mortality rate compared to the healthy female popula-

tion. Cardiovascular problems represent leading death causes.

How can the microcytic iron deficiency anemia of our patient be related to Turner syndrome?

The patient took non-steroidal anti-inflammatory drugs for intensive back pains that could be related to the vertebral compression fracture of osteoporotic origin. As she received no estrogen supplementation for decades, the origin of her osteoporosis is clear. Gastroduodenal mucosa damage is a very well-known side effect of non-steroidal anti-inflammatory drugs.

Other possible causes of iron deficiency in Turner syndrome include celiac disease (defective iron absorption), inflammatory bowel disease, and also intestinal angiodysplasias (intestinal blood loss). These could be excluded in our case.

What can be done to improve height in Turner syndrome patients?

A major feature of Turner syndrome is short stature that is manifested by an average 20 cm below the normal adult female population. Although patients with Turner syndrome are not growth hormone (GH) deficient, human recombinant GH can be administered in childhood and adolescence to increase height. It is usually given if the height of the girl is below the fifth percentile on the growth chart and treatment is usually begun between 2 and 5 years of age. The dose is around 40–50 μg/kg/day. In addition to GH, a mild anabolic steroid (non-aromatizable androgen) oxandrolone can be given at doses between 0.03 and 0.05 mg/kg to girls aged 10 or older.

Certainly, these treatment possibilities are not available in adulthood due to the epiphyseal closure.

Which hormones can be used in children with Turner syndrome to predict ovarian failure and the necessity for estrogen replacement?

Apart from FSH, anti-müllerian hormone (AMH) should be highlighted as this could be used to assess likelihood of spontaneous puberty. AMH levels are associated with oocyte numbers, and low levels indicate reduced ovarian reserve.

Is pregnancy possible in Turner syndrome patients?

About 5–7% of Turner syndrome patients have spontaneous pregnancies that are mostly seen in mosaic cases. Oocyte donation is the usual solution for pregnancy if there are no contraindications (mainly gynecological or cardiological). In some (mostly mosaic) Turner syndrome patients having ovarian reserve, cryopreservation of ovarian tissues might also be performed.

How should adult Turner syndrome patients be treated?

Adult Turner syndrome patients should receive estrogen/progestin therapy (e.g., 100 μg/day transdermal estradiol patch + daily 200 mg progesterone for 12 days of the menstrual cycle) that corresponds to the treatment of primary ovarian insufficiency (POI, discussed in ► Chap. 42). Estrogen treatment is essential for maintaining bone health and preventing osteoporosis (that developed in our patient without estrogen supplementation), cardiovascular and urogenital health. Estrogen/progestin therapy should be given till about 50 years of age.

Vitamin D should be given to Turner syndrome patients.

How should patients with Turner syndrome be followed up?

1. *Cardiology*: Regarding the high frequency of cardiovascular abnormalities, annual monitoring of blood pressure, ECG and imaging with echocardiography, or even cardiac MRI are warranted whose frequency depends upon the detected abnormalities. The most feared complication of

Turner syndrome is aortic dissection whose risk can be monitored by the aortic size index (ASI). In low-risk patients without cardiovascular abnormalities and with an ASI < 2 cm/m^2 every 5–10 years, whereas in high-risk patient even every 6–12 months.

2. *Bones*: Bone mineral density (BMD) should be measured at diagnosis and then at regular intervals depending on the initial BMD and whether the patient receives estrogen substitution. BMD can be underestimated in patients with short stature by conventional techniques. In patients with osteoporosis, annual measurements are warranted, whereas in patients with normal bone density and under estrogen replacement, BMD can be measured every 5 years.
3. *TSH* should be measured annually.
4. *Further laboratory tests* include annual fasting glucose and HBA1c and liver enzymes, and screening for celiac disease if corresponding symptoms are present. (In children, screening for celiac disease starts at 2 years of age and then continued biannually.)
5. *Audiometry* is recommended every 5 years.

Tips

- The reader is advised to read the next chapter on Primary Ovarian Insufficiency (► Chap. 41).

Take Home Messages

- Turner syndrome is a complex developmental abnormality that is one of the most common causes for primary/hypergonadotropic hypogonadism in women.
- Turner syndrome is caused by partial or complete absence of one of the X chromosomes or by other karyotypes (e.g., mosaics). About 50% of patients display the classical 45X,0 karyotype.
- Typical phenotypical features of Turner syndrome include short stature, short fourth metacarpals, shield-like chest, and webbed neck. The major clinical manifestations include ovarian failure, cardiovascular, autoimmune, renal, bone, middle ear, and ophthalmological abnormalities.
- The height of affected girls can be increased by growth hormone therapy.
- Regular, multidisciplinary follow-up of patients is warranted.

Suggested Reading

1. Backeljauw P, Klein K. Sex hormone replacement therapy for individuals with Turner syndrome. Am J Med Genet C Semin Med Genet. 2019;181(1):13–7. https://doi.org/10.1002/ajmg.c.31685.
2. Dabrowski E, Johnson EK, Patel V, Hsu Y, Davis S, Goetsch AL, Habiby R, Brickman WJ, Finlayson C. Turner Syndrome with Y Chromosome: Spontaneous Thelarche, Menarche, and Risk of Malignancy. J Pediatr Adolesc Gynecol. 2020;33(1):10–4. https://doi.org/10.1016/j.jpag.2019.08.011.
3. Donadille B, Bernard V, Christin-Maitre S. How can we make pregnancy safe for women with Turner syndrome? Am J Med Genet C Semin Med Genet. 2019;181(1):100–7. https://doi.org/10.1002/ajmg.c.31682.
4. Fuchs MM, Attenhofer Jost C, Babovic-Vuksanovic D, Connolly HM, Egbe A. Long-Term Outcomes in Patients With Turner Syndrome: A 68-Year Follow-Up. J Am Heart Assoc. 2019;8(11):e011501. https://doi.org/10.1161/jaha.118.011501.
5. Gravholt CH, Andersen NH, Conway GS, Dekkers OM, Geffner ME, Klein KO, Lin AE, Mauras N, Quigley CA, Rubin K, Sandberg DE, Sas TCJ, Silberbach M, Soderstrom-Anttila V, Stochholm K, van Alfen-van derVelden JA, Woelfle J, Backeljauw PF. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. Eur J Endocrinol. 2017;177(3):G1–g70. https://doi.org/10.1530/eje-17-0430.
6. Gravholt CH, Viuff MH, Brun S, Stochholm K, Andersen NH. Turner syndrome: mechanisms and management. Nat Rev Endocrinol. 2019;15(10):601–14. https://doi.org/10.1038/s41574-019-0224-4.
7. Kosteria I, Kanaka-Gantenbein C. Turner Syndrome: transition from childhood to adolescence. Metab Clin Exp. 2018;86:145–53. https://doi.org/10.1016/j.metabol.2017.12.016.
8. Lleo A, Moroni L, Caliari L, Invernizzi P. Autoim-

munity and Turner's syndrome. Autoimmun Rev. 2012;11(6–7):A538–43. https://doi.org/10.1016/j.autrev.2011.11.015.
9. Los E, Rosenfeld RG. Growth and growth hormone in Turner syndrome: looking back, looking ahead. Am J Med Genet C Semin Med Genet. 2019;181(1):86–90. https://doi.org/10.1002/ajmg.c.31680.
10. Mortensen KH, Young L, De Backer J, Silberbach M, Collins RT, Duijnhouwer AL, Pandya B, Gravholt CH, Lopez L, Roos-Hesselink JW. Cardiovascular imaging in Turner syndrome: state-of-the-art practice across the lifespan. Heart. 2018;104(22):1823–31. https://doi.org/10.1136/heartjnl-2017-312658.
11. Sun L, Wang Y, Zhou T, Zhao X, Wang Y, Wang G, Gang X. Glucose metabolism in Turner syndrome. Front Endocrinol. 2019;10:49. https://doi.org/10.3389/fendo.2019.00049.

Primary Ovarian Insufficiency

Attila Molvarec

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_41

Opening

In this chapter, the clinical features, diagnosis, and management of 46XX primary ovarian insufficiency (POI) are reviewed. Turner syndrome is discussed in different chapter.

Definition of the Disease

Primary ovarian insufficiency (POI) is defined as the development of primary (hypergonadotropic) hypogonadism before the age of 40 years. The age-specific incidence of 46XX POI is 1 in 250 by age 35 years and 1 in 100 by age 40 years. The disorder differs from natural menopause, as 50–75% of patients experience intermittent ovarian function and 5–10% of women conceive after initial diagnosis. Therefore, the old terms, premature ovarian failure (POF) or premature menopause, are inaccurate and not used any more for this condition. The term primary ovarian insufficiency is also less stigmatizing than older ones.

Primary ovarian insufficiency is a spectrum disorder that includes a continuum of occult (reduced fertility, normal follicle-stimulating hormone (FSH) level, and regular menses), biochemical (reduced fertility, elevated FSH level, and regular menses) and overt ovarian insufficiency (reduced fertility, elevated FSH level, irregular or absent menses) as defined in fragile X syndrome premutation carriers.

Case Presentation

A 32-year-old woman visited our gynecological endocrinology department because she has amenorrhea for 4 months. Her pubertal development was normal with menarche at 13 years of age. She had no medical disorder and was never pregnant. She did not take any medicine including oral contraceptive. She complained about hot flushes. There was no galactorrhea, acne, or hirsutism. Her body weight was 60 kg and height was 170 cm.

What kind of examinations should be performed to determine the cause of secondary amenorrhea in this patient?

A gynecological pelvic examination with transvaginal ultrasonography should be undertaken. Hormonal examinations include serum FSH, luteinizing hormone (LH), estradiol, prolactin, thyroid-stimulating hormone (TSH), testosterone, dehydroepiandrosterone sulfate (DHEAS), and serum β-human chorionic gonadotropin (hCG) measurement to exclude pregnancy.

Her serum FSH level was 45 IU/l, while her serum estradiol concentration was 15 pg/ml (these hormonal results are characteristic for postmenopausal women). Other biochemical variables were within normal range. Pelvic examination was normal with an endometrial thickness of 2 mm and β-hCG was negative.

How can the diagnosis of primary ovarian insufficiency be established?

The diagnostic criteria of POI are irregular menses (amenorrhea, oligomenorrhea, polymenorrhea, or metrorrhagia) in women before the age of 40 years in association with FSH level in the postmenopausal range as defined by the measuring laboratory (usually above 40 IU/l) on two occasions at least 4 weeks apart. In women with menstrual cycles, FSH should be determined on cycle day 3.

To avoid delay in diagnosis, young women with menstrual irregularity for at least 3 months should be evaluated for primary ovarian insufficiency.

What are the characteristic clinical features of primary ovarian insufficiency?

POI is characterized by a disturbance in menstrual pattern (amenorrhea, oligomenorrhea, polymenorrhea or metrorrhagia) and symptoms of estrogen deficiency such as hot flushes, night sweats, vaginal dryness, dyspareunia, and disordered sleep.

What are the long-term consequences of primary ovarian insufficiency?

Women with POI are at increased risk of osteopenia, osteoporosis, and osteoporotic fracture, especially if ovarian insufficiency develops in young women before they achieve peak bone mass. POI is also associated with increased cardiovascular morbidity and mortality. POI has also been linked to diminished sexual well-being, dementia, and cognitive decline. Women with POI may also develop anxiety and/or depression as a consequence of their diagnosis.

What are the known causes of primary ovarian insufficiency?

Turner syndrome (due to X monosomy or deletion in the short arm of X chromosome), other X chromosome deletions, inversions, duplications, and balanced X chromosome-to-autosome translocations are among the most common causes of POI. Fragile X syndrome premutation carriers (CGG repeat length of 55–200) have an increased risk to develop POI. The prevalence of *FMR1* premutations in women with sporadic POI is 2–5%, while that is 12–14% in familiar POI. POI is common in patients with galactosemia. Ovarian toxins such as chemotherapy (especially alkylating agents) and pelvic radiation therapy can also cause POI. Four percent of women with 46XX POI has autoimmune oophoritis (isolated or part of type 1 or type 2 polyglandular autoimmune syndromes). Steroidogenic enzyme defects, FSH receptor, and Gs-α subunit gene mutations have also been linked to POI. Several rare syndromic disorders can also present with symptoms of POI. However, the etiology of POI is unknown in 75–90% of cases (idiopathic).

In our patient, repeated FSH level was also in the postmenopausal range. How can we determine the underlying cause of primary ovarian insufficiency?

Basic evaluation of women with POI includes a karyotype analysis, testing for an *FMR1* premutation and for adrenal autoantibodies (serum adrenocortical and 21-hydroxylase antibodies to diagnose autoimmune oophoritis). Serum anti-ovarian antibody test has a poor predictive value to detect autoimmune oophoritis and is therefore not recommended. Women with spontaneous POI should be screened for anti-thyroid-peroxidase autoantibodies (anti-TPO), because they have a higher risk for autoimmune thyroiditis. Pelvic ultrasonography can reveal enlarged, multifollicular ovaries in autoimmune oophoritis or in steroidogenic enzyme defects. Genetic testing for rare disorders is not indicated, except for women with syndromic features. Ovarian biopsy does not add additional information for management of patients and is therefore not recommended. At the time of diagnosis, bone mineral density should be determined with dual-energy X-ray absorptiometry (DEXA).

In women with positive adrenal autoantibodies, basal cortisol and adrenocorticotropic hormone (ACTH) level should be measured at initial evaluation and annually. These women have a 50% risk of developing primary adrenal insufficiency. Evaluation for possible associated autoimmune diseases should be based on clinical symptoms. If adrenal autoantibodies are not present, adrenal function should be tested if clinical symptoms of adrenal insufficiency develop. In women with POI and thyroid (anti-TPO) autoantibodies, TSH should be determined every year.

We did not find an underlying cause of primary ovarian insufficiency in our patient, as in 75–90% of cases (idiopathic POI). How can we manage ovarian insufficiency of our patient?

In women with POI, systemic hormone therapy is indicated to treat symptoms of estrogen deficiency (vasomotor symptoms and urogenital atrophy), to reduce the risk of osteoporosis and cardiovascular disorders, and to improve quality of life. Full replacement doses of estrogen should be combined with progestogen therapy to pre-

vent endometrial hyperplasia and cancer. Progestins can be administered continuously or sequentially. With cyclic (sequential) regimen, pregnancy can be recognized earlier. Transdermal estrogen therapy poses a lower risk of venous thromboembolism and gallbladder disease than oral treatment. Regarding progestins, micronized progesterone is preferable as it does not exert adverse effects on lipid profile and clotting factors (▶ Box 41.1).

The oral contraceptive pill is a good option for women who are not seeking pregnancy. However, combined hormonal contraceptives are more potent preparations, and menopausal hormone therapy containing physiologic dose of estrogen seems to be more beneficial for bone mineral density.

Systemic hormone therapy should be continued until the average age of natural menopause (50–51 years of age). Local (vaginal) estrogen should be added in some patients for improvement of sexual function. Androgen therapy is not beneficial in patients with POI and can have potential side effects. Therefore, it is not recommended.

Box 41.1 Usual Doses of Hormone Therapy in Primary Ovarian Insufficiency

- *Estrogen:*
  - 1–2 mg 17β-estradiol (oral)
  - 100 μg 17β-estradiol (transdermal)
  - 0.625–1.25 mg conjugated equine estrogen (oral)
- *Progestogen:*
  - Continuous:
    - 2.5–5 mg medroxyprogesterone acetate daily (oral)
    - 100 mg micronized progesterone daily (oral or vaginal)
    - 0.5–1 mg norethisterone acetate daily (oral)
    - 20 μg levonorgestrel daily (intrauterine system)
  - Sequential (cyclic):
    - 10 mg medroxyprogesterone acetate daily (oral) for 10–12 days in each month
    - 200 mg micronized progesterone daily (oral or vaginal) for 10–12 days in each month
    - 1 mg norethisterone acetate daily (oral) for 10–12 days in each month

In our patient, bone mineral density was normal. How can we prevent osteoporosis and cardiovascular disorders?

In addition to systemic hormone therapy, women with POI should avoid smoking, take regular weight-bearing exercise, and eat a healthy diet to maintain a normal body weight. An intake of 1200 mg of elemental calcium per day and maintenance of adequate vitamin D status are also recommended. For osteoporosis treatment, bisphosphonates can be used. However, they should be avoided if pregnancy is possible.

Spontaneous ovarian activity may resume in 50–75% of patients with primary ovarian insufficiency. Which kind of contraceptive methods can be used?

Hormonal contraception can serve the dual purpose of treating estrogen deficiency and preventing pregnancy. Another option is lower, non-contraceptive dose of estrogen in combination with a levonorgestrel-releasing intrauterine contraceptive device. Barrier methods of contraception can also be used in women with POI.

What are the treatment options if our patient desires pregnancy?

Ovulation induction drugs such as gonadotropins and clomiphene citrate are ineffective. In vitro fertilization with donor oocytes or donor embryos is the most appropriate treatment. Adoption is an alternative option. Fertility preservation with oocyte cryopreservation or ovarian tissue freezing may be used in women with known genetic risk for POI (*FMR1* premutation carriers, Turner mosaics, and poly-

glandular autoimmune syndrome type 2). However, in women with established POI, this option is already missed.

We introduced cyclic hormone therapy with 17β-estradiol and norethisterone acetate to our patient. How should she be followed up?

Patients with POI using systemic hormone therapy should be clinically monitored annually including compliance. In our practice, we perform gynecological examination with transvaginal ultrasonography to determine endometrial thickness every year. We measure blood pressure and assess lipid profile, fasting plasma glucose, liver and renal function, as well as coagulation parameters every year. If the patient has osteoporosis, we determine bone mineral density with DEXA every year, otherwise every second year. Over 40 years of age, we perform mammography annually to screen for breast cancer.

Tips

The reader is advised to read the previous chapter on Turner syndrome (▶ Chap. 40), and also the chapter on Addison's disease and polyendocrine autoimmune syndrome 2 (▶ Chap. 31).

Take Home Messages

- Primary ovarian insufficiency is defined as the development of primary (hypergonadotropic) hypogonadism before the age of 40 years.
- The diagnostic criteria of POI are irregular menses in women before the age of 40 years in association with FSH level in the postmenopausal range.
- POI is characterized by a disturbance in menstrual pattern (amenorrhea, oligomenorrhea, polymenorrhea, or metrorrhagia) and symptoms of estrogen deficiency such as hot flushes, night sweats, vaginal dryness, dyspareunia, and disordered sleep.
- Women with POI are at increased risk of osteopenia, osteoporosis, and osteoporotic fracture. POI is also associated with increased cardiovascular morbidity and mortality. POI has also been linked to diminished sexual well-being, dementia, and cognitive decline.
- Basic evaluation of women with POI includes a karyotype analysis, testing for an *FMR1* premutation and for adrenal autoantibodies. Women with spontaneous POI should be screened for thyroid-peroxidase autoantibodies (anti-TPO). A pelvic ultrasonography and measurement of bone mineral density with DEXA are also indicated at the time of diagnosis.
- In women with POI, systemic hormone therapy should be applied until the average age of natural menopause (50–51 years of age) to treat symptoms of estrogen deficiency, to reduce the risk of osteoporosis and cardiovascular disorders, and to improve quality of life. Hormonal contraception can serve the dual purpose of treating estrogen deficiency and preventing pregnancy.
- If the patient desires pregnancy, in vitro fertilization with donor oocytes or donor embryos is the most appropriate treatment. Adoption is an alternative option.

Suggested Reading

1. Committee on Adolescent Health Care. Committee Opinion No. 605: Primary ovarian insufficiency in adolescents and young women. Obstet Gynecol. 2014;124(1):193–7. https://doi.org/10.1097/01.AOG.0000451757.51964.98.
2. Committee on Gynecologic Practice. Committee Opinion No. 698: Hormone therapy in primary ovarian insufficiency. Obstet Gynecol. 2017;129(5):e134–41. https://doi.org/10.1097/AOG.0000000000002044.
3. European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI,

Webber L, Davies M, Anderson R, Bartlett J, Braat D, Cartwright B, Cifkova R, de Muinck Keizer-Schrama S, Hogervorst E, Janse F, Liao L, Vlaisavljevic V, Zillikens C, Vermeulen N. ESHRE Guideline: management of women with premature ovarian insufficiency. Hum Reprod. 2016;31(5):926–37. https://doi.org/10.1093/humrep/dew027.

4. Nelson LM. Clinical practice. Primary ovarian insufficiency. N Engl J Med. 2009;360(6):606–14. https://doi.org/10.1056/NEJMcp0808697.
5. Welt CK. Primary ovarian insufficiency: a more accurate term for premature ovarian failure. Clin Endocrinol (Oxf). 2008;68(4):499–509. https://doi.org/10.1111/j.1365-2265.2007.03073.x.
6. Welt CK. In: Post TW, editor. Clinical manifestations and diagnosis of spontaneous primary ovarian insufficiency (premature ovarian failure). Waltham: UpToDate; 2020. https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-spontaneous-primary-ovarian-insufficiency-premature-ovarian-failure.
7. Welt CK. In: Post TW, editor. Pathogenesis and causes of spontaneous primary ovarian insufficiency (premature ovarian failure). Waltham: UpToDate; 2020. https://www.uptodate.com/contents/pathogenesis-and-causes-of-spontaneous-primary-ovarian-insufficiency-premature-ovarian-failure.
8. Welt CK. In: Post TW, editor. Management of spontaneous primary ovarian insufficiency (premature ovarian failure). Waltham: UpToDate; 2020. https://www.uptodate.com/contents/management-of-spontaneous-primary-ovarian-insufficiency-premature-ovarian-failure.

Klinefelter Syndrome

Nikolette Szücs

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_42

Opening

In this chapter the reader will be informed about the specific clinical features, diagnosis, and treatment of Klinefelter syndrome (KS), a congenital form of hypergonadotropic/primary hypogonadism.

Definition of the Disease

Klinefelter syndrome (KS) is the most frequent chromosomal aberration in males, occurring in 1:500 males, and is associated with primary hypogonadism and infertility.

The disease is typically associated with decreased total testosterone level and elevated gonadotropin levels (LH [luteinizing hormone] and FSH [follicle-stimulating hormone]), and it is the most common cause of primary or hypergonadotropic hypogonadism in males.

The molecular basis of Klinefelter syndrome is related to the presence of one or more supernumerary X chromosomes. Approximately 80–85% of cases are due to a single supernumerary X chromosome (47,XXY), while the remaining 15–20% are related to multiple aneuploidies (48,XXXY, 48,XXYY, etc.), but mosaic forms may also occur. Mosaicism means that multiple cell lines with different genetic composition are present in the body (e.g., 47,XXY/46XY). Some mosaic forms are associated with milder phenotypes.

KS is severely underdiagnosed or it is diagnosed late in life. Due to numerous comorbidities, a life-long care is needed.

Case Presentation

A 50-year-old man was referred to our department complaining of decreased libido and general fatigue. Moderate erectile dysfunction and sustained morning spontaneous erection has been reported.

The previously performed total serum testosterone (T) concentration was low (T: 4.8 nmol/l; normal range: 10.4–34.7 nmol/l).

Repeated total testosterone (2.07 ng/ml; normal: 2.8–8.0) and free testosterone (31.85 pg/mL; normal: 65.00–250.00) were both low, with elevated LH (20.86 IU/l; normal: 0.7–8.6) and FSH (28.44 IU/L; normal: 1.5–12.4) levels.

Is it sufficient to measure serum testosterone once?

Testosterone levels are quite variable; therefore, if initial test results are low, repeated measurements are recommended in 2–3 weeks in the morning.

What are the characteristics of this case that make us suspect Klinefelter syndrome?

The patient complained of erectile dysfunction and decreased libido. By physical examination, truncal obesity, decreased facial and pubic hair, symmetric gynecomastia (Fig. 42.1) without galactorrhea, and small (8 ml), firm bilateral testes were found.

The major clinical abnormalities associated with Klinefelter syndrome are presented in Table 42.1.

In infancy, other main symptoms include learning disabilities, psychiatric disturbances, and delay of speech development.

How should the diagnosis of Klinefelter syndrome be confirmed?

The diagnosis is based on the analysis of the chromosomal karyotype. The patient's karyogram was the typical 47XXY (Fig. 42.2).

What is the difference between primary and secondary hypogonadism?

Primary hypogonadism is caused by a disease of the testicles, and therefore, gonadotropins are elevated due to the feed-back regulation of the hypothalamo-pituitary-

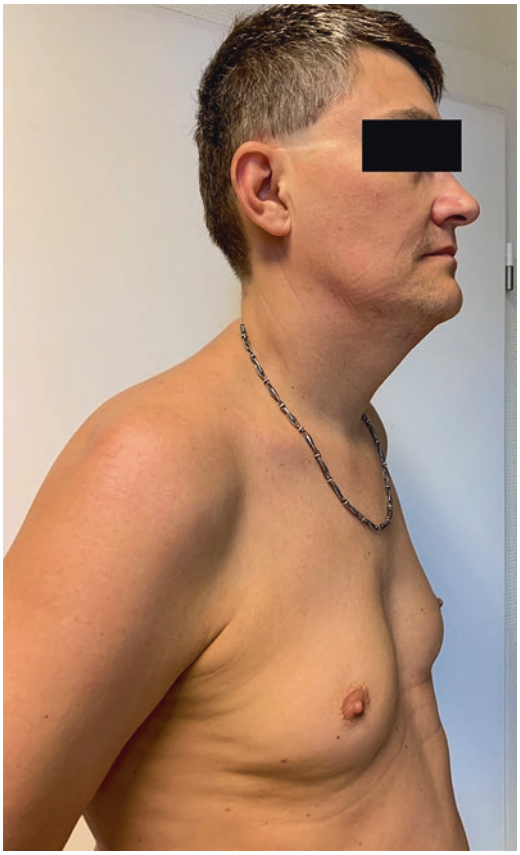

Fig. 42.1 Symmetric gynecomastia in the patient

gonad axis. Primary hypogonadism is therefore hypergonadotropic. On the other hand, secondary hypogonadism is caused by pituitary malfunctioning, and thus, gonadotropins are low (hypogonadotropic). (Similar distinctions are valid for primary and secondary adrenal insufficiency and hypothyroidism, as well.)

What kind of diseases/conditions can be related to gynecomastia?

Gynecomastia is defined as a benign hyperplasia of glandular breast tissue in men. It should be differentiated from lipomastia that is related to increased breast fat tissue in obesity. Physiological gynecomastia is often seen in puberty.

Table 42.1 Major abnormalities of adult KS and estimated occurrence

Abnormalities	Frequency
Infertility, azoospermia	90–95%
Small testes (<8 mL)	95–99%
Increased gonadotropin levels	95–99%
Decreased testosterone levels	60–85%
Gynecomastia	40–75%
Decreased facial, pubical hair	30–80%
Decreased bone mineral density	10–40%
Mitral valve prolapse	0–55%
Metabolic syndrome	45%
Increased height	30%
Learning disability	0–70%
Low muscle mass/increased fat mass	40–50%
Breast cancer	Increased risk (50-fold)

Gynecomastia is a common feature related to estrogen excess and/or androgen deficiency and can be seen in a variety of endocrine-related disorders (e.g., primary hypogonadism, testicular tumors, estrogen-secreting adrenal tumors, hCG-secreting tumors, disorders of sexual differentiation [DSD], and hyperprolactinemia).

Non-endocrine illnesses, including liver failure and chronic kidney disease, and many medications are also common causes of gynecomastia. These include drugs having anti-androgenic properties (e.g., spironolactone), inhibitors of steroid biosynthesis (e.g., ketoconazole), 5α-reductase inhibitor (finasteride), estrogen derivatives, but even histamine H2 receptor blocker (cimetidine) and proton-pump inhibitor (omeprazole), angiotensin converting enzyme inhibitor and digoxin among many others.

KS patients are usually taller than average. What can be the mechanism?

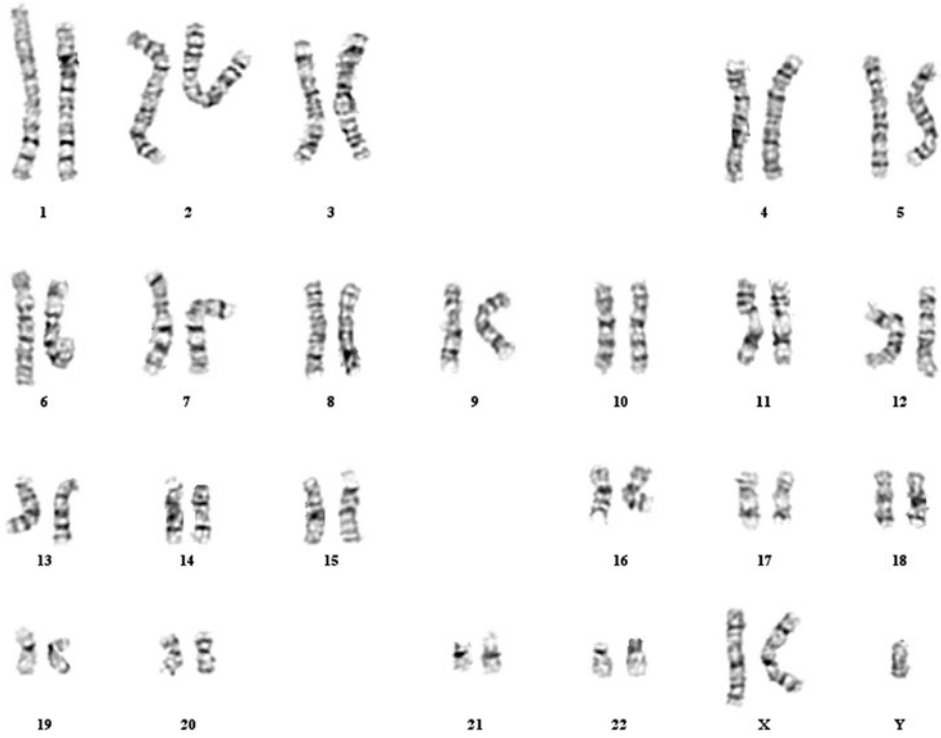

Fig. 42.2 Karyogram of the KS patient with a supernumerary X chromosome (47,XXY). (Courtesy of Dr. Irén Haltrich (2nd Department of Pediatrics, Semmelweis University))

This observation can be related to two pathomechanisms. Due to hypogonadism, the epiphyseal closure is delayed, and therefore, patients can grow for longer; moreover, the double X chromosome harboring genes responsible for growth promotion might also have a role.

What kind of other main causes of male primary hypogonadism are important to mention?

► Box 42.1 presents the other major causes of primary hypogonadism in males.

Box 42.1 Other Major Causes of Primary Hypogonadism in Males

- Undescended or ectopic testes
- Secondary testicular dysfunction-medications, toxins, irradiation
- Acquired or congenital anorchia (trauma, tumor, torsion, surgical removal)
- Orchitis (viral, e.g., mumps, or unspecific orchitis)
- Enzymatic defects of steroid biosynthesis – 46,XY DSD
- 46,XX male-translocation of the SRY region to the X chromosome
- Noonan syndrome[a]
- Inactivating LH receptor mutations – Leydig cell hypoplasia

Abbreviations:

DSD disorder of sexual development, *SRY* Sex determining Region of Y Chromosome

[a]Noonan syndrome is an autosomal dominantly inherited disease with heterogeneous genetic background associated with short stature and heart defects, also sometimes termed as male Turner syndrome

Back to Our Patient

Considering his complaints and laboratory test results, and his lack of intention for having children, testosterone replacement was introduced in a transdermal form (daily 50 mg testosterone gel).

We can choose between the daily transdermal form, which mimics the physiological secretion of the testosterone, and a long-acting depot injection form, which can be more convenient for some patients.

How should the treatment be adjusted in Klinefelter syndrome?

The treatment and care of patient with Klinefelter syndrome needs a multidisciplinary collaboration among psychologists, pediatricians, general practitioners, and specialists for endocrinology, urology, and infertility.

The goal of testosterone replacement therapies is to return serum testosterone levels to within the physiological range, and thereby to promote the development of secondary male sexual characteristics.

Some men who suffer from severe gynecomastia may require cosmetic surgical intervention.

The clinical effectiveness and safety of androgen replacement therapy should be checked every 3 months after launching the treatment for 1 year and then annually.

What are the major side effects of testosterone replacement therapy?

Among the possible side effects, we must emphasize the elevation of hemoglobin levels due to increased erythrocytosis. This can be alleviated by dose reduction or periodical venesection. Monitoring the liver functions between 6 and 12 months and annual abdominal ultrasound examinations are needed for assessing potential hepatotoxicity. Hepatotoxicity, however, is mostly seen with the rarely given oral testosterone.

Moreover, annual control of the PSA (prostate-specific antigen) level and urological examination are also recommended.

Can patients with Klinefelter syndrome have children?

Men with Klinefelter syndrome have impaired fertility and are mostly azoospermic. Thus, in general, most Klinefelter syndrome patients are infertile. KS patients with mosaic karyotypes might have reduced fertility. The advent of novel assisted reproductive techniques such as the surgical extraction of sperm from testes (testicular extraction of sperm [TESE] or microscopic TESE [microTESE]) might help some KS patients to have children. This technique, however, must be done at such a young age as possible, and the sperm should be cryopreserved. Intracytoplasmatic sperm injection (ICSI) can then be implemented, and thus, patients who were previously considered to be infertile now might have children.

In our case, the syndrome was diagnosed at the age of 50 years, and at this age, due to the progressive testicular damage in KS, the retrieval of sperm is generally unsuccessful.

Do KS patients need a life-long hormone replacement?

Klinefelter syndrome usually means a life-long testosterone replacement.

What are the dangers of long-term hypogonadism?

In long-standing untreated hypogonadism, the cardiovascular morbidity is higher due to the insulin resistance and abnormal body composition (lean body mass decreased

and elevated fat mass), and decreased bone mineral density leads to osteopenia or osteoporosis and associated increased risk of fracture.

Osteodensitometry in our case showed osteopenia (T-score −1.4 at the lumbar spine, −0.4 at left femoral neck, and −2.1 at left radius distal 1/3.) Echocardiography and chest X-ray were normal. His cholesterol, triglyceride (TG) and glucose, HbAIC level were in the normal ranges.

What comorbidities are frequent in Klinefelter syndrome?

Patients with KS may have an increased risk for diabetes mellitus, hypothyroidism, hypoparathyroidism, autoimmune diseases (systemic lupus erythematosus, Sjogren's syndrome, and rheumatoid arthritis), osteopenia, osteoporosis, bronchitis, obstructive bronchial disease, and breast cancer.

What is the risk for breast cancer in KS patients?

Whereas male breast cancer in the normal population is extremely rare, KS patients have a 50-fold increased risk. However, the life-time risk for breast cancer is low (<1%).

Does Klinefelter syndrome affect the life expectancy of patients?

Yes, the mortality of KS patients is increased because of the associated cardiovascular, hemostatic, and metabolic complications.

We must also emphasize that their quality of life is worse than that of the general population.

Tips

The reader is advised to read the chapter on Kallmann syndrome (hypogonadotropic hypogonadism).

Take Home Messages

- Klinefelter syndrome is the most frequent chromosomal aberration in males, and it is also the most common cause of primary hypogonadism in males.
- KS is associated with primary/hypergonadotropic hypogonadism of varying severity, but infertility is common.
- Life-long testosterone replacement to prevent osteoporosis, obesity, metabolic syndrome, and diabetes is warranted.
- Life-long care is needed due to numerous comorbidities.

Suggested Reading

1. Bonomi M, Rochira V, Pasquali D, Balercia G, Jannini EA, Ferlin A, Klinefelter ItaliaN Group (KING). Klinefelter syndrome (KS): genetics, clinical phenotype and hypogonadism. J Endocrinol Invest. 2017;40(2):123–34. https://doi.org/10.1007/s40618-016-0541-6.
2. Groth KA, Skakkebæk A, Høst C, Gravholt CH, Bojesen A. Clinical review: Klinefelter syndrome-A clinical update. J Clin Endocrinol Metab. 2013;98(1):20–30. https://doi.org/10.1210/jc.2012-2382.
3. Kanakis GA, Nieschlag E. Klinefelter syndrome: more than hypogonadism. Metabolism. 2018;86:135–44. https://doi.org/10.1016/j.metabol.2017.09.017.
4. Radicioni AF, Ferlin A, Balercia G, Pasquali D, Vignozzi L, Maggi M, Foresta C, Lenzi A. Consensus statement on diagnosis and clinical management of Klinefelter syndrome. J Endocrinol Invest. 2010;33(11):839–50. https://doi.org/10.1007/BF03350351.
5. Shiraishi K, Matsuyama H. Klinefelter syndrome: from pediatrics to geriatrics. Reprod Med Biol. 2018;18(2):140–50. https://doi.org/10.1002/rmb2.12261.

Complete Androgen Insensitivity Syndrome

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Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_43

Opening

In this chapter, the clinical features, diagnosis, and treatment of complete androgen insensitivity syndrome (CAIS) are presented. CAIS is a rare disease belonging to the disorders of sex development (DSD), which is a cause for primary amenorrhea in women. CAIS is caused by various mutations in the androgen receptor (AR) gene

Definition of the Disease

Complete androgen insensitivity syndrome (CAIS) can be defined as hormone resistance to androgens resulting in a female phenotype in an individual with a normal male 46,XY karyotype and testes producing age-appropriate normal concentrations of androgens (testosterone) (46,XY DSD). It can also be categorized as a form of sex reversal, since a female phenotype develops despite a normal male karyotype. Previously, the term male pseudohermaphroditism was also used for describing such syndromes where the affected individual has testes, but female external genitalia or a complete female phenotype like in CAIS is present.

Other forms of AIS (androgen insensitivity) include mild AIS (MAIS) and partial AIS (PAIS). The etiopathogenesis is related to mutations in the X-linked androgen receptor gene. This syndrome was described by John Morris in 1953 based on 82 cases. He named this syndrome "testicular feminization syndrome." It reflected the observation that testes in these patients produced a hormone that had a feminizing effect on the body. At present, it is understood that it results from the subsequent aromatization of testosterone into estrogen. In the past, other names to describe this syndrome were also used, namely, Morris' syndrome and Goldberg-Maxwell syndrome. After the understanding of the underlying molecular pathogenesis (defects in the androgen receptor) of this syndrome, the currently accepted name is androgen insensitivity syndrome. Complete AIS is rare and occurs in as many as 1 in 20,000 live births. About two-thirds of CAIS are inherited from the mother as an X-linked recessive trait, and one-third present as de novo, sporadic mutations. Patients with CAIS are infertile.

Case Presentation

A 44-year-old Caucasian female was referred to the Department of Gynecological Endocrinology, Poznan University of Medical Sciences, due to primary amenorrhea. It is rare to diagnose primary amenorrhea in a patient at this age. Nevertheless, she had never requested diagnostic examinations before admission. She did not have any relevant past medical or family history.

What relevant clinical characteristics were found during the examination of the patient?

The patient had normal breast development (Tanner stage 5) and poor pubic hair (Tanner stage 1). She had no axillary hair. Her weight on admission was 98 kg, her height was 164 cm, and her BMI was 36.5 kg/m^2. Gynecological examination and transvaginal ultrasound revealed a blind-ended hypoplastic vagina with 3 cm of depth and the complete lack of uterus and ovaries. External genitalia were completely female. Urography revealed no abnormalities of the urinary tract.

Which clinical characteristics are the most important for CAIS diagnosis?

The diagnosis, which is typically made in an adolescent or young adult woman, is based upon a constellation of clinical and biochemical findings, including the following:

- Female phenotype with normal breast development
- Primary amenorrhea
- Little or no axillary or pubic hair
- Absent uterus, but testes present
- Blind vaginal pouch on examination

Which hormones should be measured?

The most important hormonal parameter measured in a case of suspicion of CAIS is testosterone (T). In CAIS patients, serum testosterone concentrations are either within or above the normal range for males. Luteinizing hormone (LH) concentrations are inappropriately elevated due to the fallout of negative feedback by T via the AR. Levels of follicle stimulating hormone (FSH) and inhibin can be normal, as the secretion of FSH is predominantly regulated by inhibins produced by testicular cells and is therefore less influenced by androgen insensitivity.

What were the hormonal results of our patient?

Serum LH, FSH, and total testosterone concentration were significantly elevated, while estradiol serum concentration was considerably low for a female. The other hormonal results were within normal limits (Table 43.1). Taking into consideration the described results, androgen insensitivity syndrome was suspected.

What additional diagnostic tests should be undertaken?

In CAIS, the testes may be located in the abdomen or in the inguinal region due to the lack of androgen action. It has been established that androgens mediate the inguinoscrotal phase of testis descent to ensure that the testes are in the scrotum at or soon after birth in humans. The site and size of the testes can be determined by ultrasonography or magnetic resonance imaging (MRI).

Table 43.1 Hormonal profile of patient on admission to hospital

	Hormonal results at diagnosis	Reference values for females
FSH [mIU/mL]	45.26	3.50–12.50[a]
LH [mIU/mL]	69.11	2.40–12.60[a]
Estradiol [pg/mL]	22.10	12.50–166.0[a]
Testosterone [ng/mL]	6.12	0.06–0.82
DHEAS [µmol/L]	4.54	1.65–9.15
TSH [µIU/mL]	1.45	0.27–4.20
FT4 [ng/dL]	0.98	0.93–1.70
Insulin [mIU/mL]	6.89	2.60–24.90

[a]Normal ranges for the follicular phase of the menstrual cycle

What was the result of diagnostic imaging in our patient?

A small pelvis MRI was performed that confirmed the absence of a uterus and ovaries; moreover, an adequately developed distal vagina was also noted. MRI did not reveal any additional pathology or masses within the pelvis. Because of the strong suspicion of AIS, we performed examinations focused on a search for testes. An ultrasound of the inguinal canals was then performed, which revealed the presence of two oval, homogenously echogenic structures bilaterally below the superficial inguinal rings (right 43 × 24 × 21 mm, left 29 × 21 × 20 mm). A follow-up contrast-enhanced pelvic MRI was performed to visualize the inguinal canals. Two homogenous contrast-enhancing solid mass lesions were confirmed bilaterally in the distal canals. It was determined that these lesions most likely corresponded to the

undescended testes. On the basis of these clinical findings, biochemical parameters, and diagnostic imaging, the patient was referred for surgery. She underwent surgical excision of both inguinal masses.

What was the histopathological result of the excised masses?

The seminiferous tubules located in the excised gonads contained only Sertoli cells. There were numerous Leydig cells in the stroma. Within the right gonad, a nodule composed of hypoplastic seminiferous tubules with immature Sertoli and Leydig cells was present (Sertoli-Leydig hamartoma). The whole microscopic image corresponded to the clinical diagnosis of androgen insensitivity syndrome.

Why was gonadectomy needed?

Prophylactic gonadectomy has been performed because of the risk for developing gonadal malignancy, mostly germ cell tumors (gonadoblastoma or dysgerminoma). The risk is low below the age of 25 years and tumor formation is most frequent between 30 and 50 years of age. An estimated average of 5% CAIS patients develop gonadal tumors.

Is genetic testing necessary for establishing the diagnosis?

The AR is coded by a single-copy gene on the X chromosome. A diagnosis of CAIS can be confirmed by sequencing the coding region of this gene. Loss-of-function mutations in the coding sequence of the AR can be found in most women with CAIS.

What was the result of genetic testing in our patient?

Chromosomal analysis (using GTG banding) confirmed a 46,XY karyotype. We have sequenced the coding AR region. A novel single base substitution from cytosine to thymine at position 66,942,710 was identified that predicted pathological effect in the Mutation Taster web application (► http://www.mutationtaster.org/).

What was the follow-up of our patient?

The patient is leading a well-adjusted life as a woman and is a fully functioning member of society. After surgical removal of both testes, she was administered hormone replacement therapy (HRT). Due to the lack of a uterus, monotherapy with estradiol 2 mg per os daily was started. Serum FSH and estradiol concentrations were measured at 1 year follow-up after surgery (◘ Table 43.2). To this day, the patient remains under our control and her health condition remains stable.

What kind of other causes of primary amenorrhea should be mentioned?

◘ **Table 43.2** Hormonal profile of patient 1 year after surgery on hormonal replacement therapy (HRT)

	After surgery; on HRT	Reference values for females
FSH [mIU/mL]	21.30	3.50–12.50[a]
LH [mIU/mL]	10.40	2.40–12.60[a]
Estradiol [pg/mL]	73.10	12.50–166.0[a]
Testosterone [ng/mL]	0.23	0.06–0.82
DHEAS [µmol/L]	9.90	1.65–9.15
TSH [µIU/mL]	1.40	0.27–4.20
FT4 [ng/dL]	1.09	0.93–1.70
Insulin [mIU/mL]	7.45	2.60–24.90
AMH [ng/mL]	<0.01	

[a]Normal ranges for the follicular phase of the menstrual cycle

- *Turner syndrome* is the most common cause of primary amenorrhea in women and it is discussed in ► Chap. 40.

- *Pure Gonadal Dysgenesis (Swyer syndrome)*

- Patients with Swyer syndrome, another syndrome of sex reversal, also referred to as pure gonadal dysgenesis (karyotype 46,XY), are clinically characterized by a delay in puberty, normal or increased height, and primary amenorrhea. They only have a streak gonad and there is a lack of the prenatal synthesis of AMH (anti-Müllerian hormone) and testosterone, leading to the preservation of the Müllerian structures (uterus, fallopian tubes, upper third of the vagina) and the atresia of the Wolffian duct. It is a very rare syndrome (estimated prevalence 1:80,000–100,000) and has been related to mutations in a number of different genes. In the perineal area, transition of the urogenital sinus into the urethra and the lower two-thirds of the vagina occurs, as well as formation of the clitoris from the genital tubercle and the development of the labia majora from urogenital swelling. As a result, the external genitals are female. Laboratory investigations show hypergonadotropic (primary) hypogonadism, with high serum concentrations of FSH, LH, and low serum concentrations of estradiol and AMH. The presence of a Y chromosome may be a risk factor for the development of tumors, such as gonadoblastoma and dysgerminoma within the gonadal tissue with a prevalence of 14–45%. Management of those patients is based on the preventive excision of streak gonads and long-term hormone replacement therapy.

- *Mayer-Rokitansky-Küster-Hauser Syndrome (MRKH syndrome)*

- Patients with Mayer-Rokitansky-Küster-Hauser syndrome lacks a uterus and a vagina due to the absence of Müllerian duct development. They have normal female gonads, normal female phenotype with pubic and axillary hair, normal breast development, and internal female genitalia. Their karyotype is 46,XX and the serum concentrations of FSH, LH, AMH, and estradiol are within the normal range. In 2015, the first live births were reported after uterus transplantation in women with MRKH syndrome.

- *Kallmann syndrome* is a hereditary form of hypogonadotropic hypogonadism associated with anosmia/hyposmia that is discussed in ► Chap. 7.

- *Enzyme Deficiencies*

- Deficiency of 5-α reductase or other enzymes (cholesterol side chain cleavage enzyme – gene *CYP11A1*, 3ß-hydroxysteroid dehydrogenase 2 – gene *HSD3B2*, 17α-hydroxylase/17,20-lyase – gene *CYP17A1* (► Chap. 35), StAR – gene *StAR*) can also lead to sexual ambiguity and must be differentiated in particular from partial AIS (PAIS) and mild AIS (MAIS).

- **Is androgen insensitivity syndrome always characterized by a female phenotype?**

- The clinical presentation of androgen insensitivity is associated with the degree of tissue resistance to the biological actions of androgens. Complete androgen insensitivity syndrome (CAIS) results in a female phenotype. Affected women (including some models and actresses) are taller than the average.

- Partial androgen insensitivity syndrome (PAIS) includes phenotypes of various degrees of masculinization in relation to AR mutations resulting in different responsiveness of external genitalia to androgens. Patients with PAIS may have both male and female physical characteristics (DSD). Typical phenotypes are associated with micropenis, severe hypospadias, and bifid scrotum. Sequencing of the AR gene is necessary to confirm the diagnosis of PAIS and to distinguish the syndrome from

other causes of undermasculinization such as partial gonadal dysgenesis, mutations of the luteinizing hormone receptor, enzyme deficiencies, or Klinefelter syndrome (▶ Chap. 42).

Mild androgen insensitivity syndrome (MAIS) also results from a mutation of the androgen receptor gene but is not associated with genital anomalies and therefore is infrequently reported. MAIS can present in men as infertility and gynecomastia. There is a form of MAIS related to Kennedy's disease that is characterized by the weakness and wasting of bulbar, facial, and limb muscles (bulbar and spinal muscular atrophy). Kennedy's disease is caused by a trinucleotide repeat expansion in the AR gene.

What kind of treatment options can be envisaged for patients?

Management of complete androgen insensitivity syndrome includes gonadectomy and subsequent hormone replacement and creation of a functional vagina. Genetic counseling and psychological care should also be provided. The primary treatment is laparoscopic gonadectomy because of a risk of gonadal malignancy, mostly germ cell tumors (gonadoblastoma or dysgerminoma). Choosing the right time for a gonadectomy is also very important from the psychological point of view. Most AIS guidelines recommend to perform gonadectomy only after the sexual characteristics are fully developed or the patient is over 16 years of age with full breast development. Other authors suggest to perform a gonadal biopsy as soon as AIS is diagnosed and propose prepubertal gonadectomy if precancerous lesions or in situ carcinomas are found. Estrogen replacement is needed to induce puberty or to maintain secondary sex characteristics. HRT is not only necessary for the development of sexual characteristics but is also a preventive option that affects later complications, such as osteoporosis and cardiovascular disease. Bone mineral density can be significantly lower in patients with CAIS that can also be improved by the administration of estrogens. Progesterone is not indicated due to the absence of a uterus. Some women suffering from CAIS prefer to take supplementary testosterone too after gonadectomy as it might improve their overall well-being including sexual desire.

Is there any adjuvant therapy that should be considered?

Psychological care and support seem to be crucial for parents and especially for children diagnosed with CAIS. Making the diagnosis affects the life of the whole family. Parents have to decide the gender their child should be raised in. Children with CAIS are mostly brought up as females. The struggle is greater with children with PAIS. Children may later need complex psychological support, especially if the gender their parents decide upon does not match their gender identity.

Tips

The reader is advised to read the chapter on Turner syndrome (▶ Chap. 40) and also the chapter on Kallmann syndrome (▶ Chap. 7) as a prototype of hypogonadotropic hypogonadism.

Take Home Messages

- Androgen insensitivity syndrome (AIS), resulting from androgen receptor dysfunction, is an important cause of disorders of sex development (DSD).
- AIS phenotypes include complete, partial, and mild forms that are associated with various degrees of residual androgen receptor activity.
- In the complete androgen insensitivity syndrome (CAIS), a female phenotype is found in a patient with a male 46,XY karyotype and testes associated with an

age-appropriate normal male concentration of testosterone.
- Imaging tests in CAIS can reveal a short vagina, absence of the uterus, or the presence of Müllerian or Wolffian duct remnants. The gonads in CAIS are invariably testes that can be located within the abdomen or labia but are most frequently found in the inguinal canals.
- Management of CAIS includes gonadectomy because of the risk of gonadal tumors in later life and hormone replacement therapy after the operation.
- Psychosocial support is central to the multidisciplinary approach for the management of androgen insensitivity syndrome.

Suggested Reading

1. Batista RL, Costa EMF, Rodrigues AS, Gomes NL, Faria JA Jr, Nishi MY, Arnhold IJP, Domenice S, Mendonca BB. Androgen insensitivity syndrome: a review. Arch Endocrinol Metab. 2018;62:227–35. https://doi.org/10.20945/2359-3997000000031.
2. Chan Y-M, Hannema SE, Achermann JC, Hughes IA. Disorders of sex development. In: Melmed S, Koenig R, Rosen C, Auchus R, Goldfine A, editors. Williams textbook of endocrinology. 14th ed. Philadelphia: Saunders Elsevier; 2019. p. 867–936.
3. Gava G, Mancini I, Orsili I, Bertelloni S, Alvisi S, Seracchioli R, Meriggiola MC. Bone mineral density, body composition and metabolic profiles in adult women with complete androgen insensitivity syndrome and removed gonads using oral or transdermal estrogens. Eur J Endocrinol. 2019;181:711–8. https://doi.org/10.1530/eje-19-0383.
4. Hughes IA, Davis John D, Bunch TI, Pasterski V, Mastroyannopoulou K, MacDougall J. Androgen insensitivity syndrome. Lancet. 2012;20:1419–28. https://doi.org/10.1016/SO140-6736(12)60071-3.
5. Hughes IA, Werner R, Bunch T, Hiort O. Androgen insensitivity syndrome. Semin Reprod Med. 2012;30:432–42. https://doi.org/10.1055/s-0032-1324728.
6. Ismail-Pratt IS, Bikoo M, Liao LM, Conway GS, Creighton SM. Normalization of the vagina by dilator treatment alone in complete androgen insensitivity syndrome and Mayer-Rokitansky-Kuster-Hauser syndrome. Hum Reprod. 2007;22:2020–4. https://doi.org/10.1093/humrep/dem074.
7. Ko JKY, King TFJ, Williams L, Creighton SM, Conway GS. Hormone replacement treatment choices in complete androgen insensitivity syndrome: an audit of an adult clinic. Endocr Connect. 2017;6:375–9. https://doi.org/10.1530/EC-17-0083.
8. Kosti K, Athanasiadis L, Goulis DG. Long-term consequences of androgen insensitivity syndrome. Maturitas. 2019;127:51–4. https://doi.org/10.1016/j.maturitas.2019.06.004.
9. Lanciotti L, Cofini M, Leonardi A, Bertozzi M, Penta L, Esposito S. Different clinical presentations and management in complete androgen insensitivity syndrome (CAIS). Int J Environ Res Public Health. 2019;16(7):1268. https://doi.org/10.3390/ijerph16071268.
10. Looijenga LH, Hersmus R, Oosterhuis JW, Cools M, Drop SL, Wolffenbuttel KP. Tumor risk in disorders of sex development (DSD). Best Pract Res Clin Endocrinol Metab. 2007;21:480–95. https://doi.org/10.1016/j.beem.2007.05.001.
11. Mendoza N, Motos MA. Androgen insensitivity syndrome. Gynecol Endocrinol. 2013;29(1):1–5. https://doi.org/10.3109/09513590.2012.705378.
12. Michala L, Goswami D, Creighton SM, Conway GS. Swyer syndrome: presentation and outcomes. BJOG. 2008;115:737–41. https://doi.org/10.1111/j.1471-0528.2008.01703.x.
13. Mongan NP, Tadokaro-Cuccaro R, Bunch TI, Hughes IA. Androgen insensitivity syndrome. Best Pract Res Clin Endocrinol Metab. 2015;29:569–80. https://doi.org/10.1016/j.beem.2015.04.005.
14. Oakes MB, Eyvazzadeh AD, Quint E, Smith YR. Complete androgen insensitivity syndrome – a review. J Pediatr Adolesc Gynecol. 2008;21:305–10. https://doi.org/10.1016/j.jpag.2007.09.006.
15. Pittock ST, Babovic-Vuksanovic D, Lteif A. Mayer-Rokitansky-Küster-Hauser anomaly and its associated malformations. Am J Med Genet A. 2005;135:314–6. https://doi.org/10.1002/ajmg.a.30721.

Neuroendocrine Tumors and Paraneoplastic Endocrine Syndromes

Neuroendocrine tumors comprise a heterogeneous group of tumors originating from the complex neuroendocrine system. Tumors originating from neuroendocrine organs such as the adrenal medulla (pheochromocytoma) or pituitary are discussed in other parts of the book. This part discusses tumors originating from dispersed neuroendocrine cells from the gastrointestinal tract (► Chap. 44 – small intestine, ► Chap. 46 – insulinoma (pancreas), and ► Chap. 48 – gastrinoma) and bronchi (► Chap. 45 – bronchial neuroendocrine tumor). The incidence of neuroendocrine tumors is growing as well as their clinical relevance. Neuroendocrine (and other) tumors can be associated with paraneoplastic endocrine syndromes. The definition of ***paraneoplastic syndrome*** refers to the condition when the tumor-associated symptoms are not in relation to the tumor mass, growth, invasion, or metastases, but the tumor secretes soluble mediators or induces autoimmune reactions that can produce symptoms in remote organs. Such soluble mediators can be hormones (paraneoplastic endocrine syndromes), but other mediators such as growth factors and cytokines can also be produced, leading to a wide variety of sometimes unusual syndromes (paraneoplastic neurologic, dermatologic, hematologic syndromes, etc.). This part discusses neuroendocrine tumors and associated syndromes, that is, carcinoid syndrome (► Chap. 44), ectopic ACTH syndrome (a severe form of hypercortisolism, ► Chap. 45), and duodenopancreatic neuroendocrine tumors (insulinoma (► Chap. 46) and gastrinoma (► Chap. 48)). ► Chapter 47 is dedicated to factitious hypoglycemia that can cause differential diagnostic problems with insulinoma.

► Chapter 49 presents humoral hypercalcemia of malignancy, which is the most common paraneoplastic endocrine syndrome in solid tumors, often resulting in life-threatening hypercalcemia. The management of hypercalcemia is also discussed here. The syndrome of inappropriate antidiuretic hormone production (SIADH), which can also be of paraneoplastic origin and considered to be the second most common paraneoplastic endocrine syndrome, is presented in the part Diseases of the Pituitary and Hypothalamus (► Chap. 10).

Contents

Carcinoid Syndrome Caused by a Small Intestinal Neuroendocrine Tumor

Peter Igaz

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_44

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Opening

The neuroendocrine system is a complex system comprised of neuroendocrine organs (e.g., the adrenal medulla, pituitary, and parathyroids) and widely dispersed neuroendocrine cells that are found in various organs, most notably in the mucosa of the gastrointestinal and respiratory tracts. Neuroendocrine tumors (NETs) can arise both in neuroendocrine organs (e.g., pheochromocytoma) and from dispersed neuroendocrine cells in other organs. The term neuroendocrine tumor that is widely used in clinical practice is mostly related to tumors arising from the dispersed neuroendocrine cells, and the well-differentiated forms of these neuroendocrine tumors were formerly termed carcinoids. The term neuroendocrine neoplasm (NEN) comprises both neuroendocrine tumors and neuroendocrine carcinoma (NEC). Carcinoid syndrome is a paraneoplastic endocrine syndrome mostly observed in patients suffering from neuroendocrine tumors of small intestinal (midgut) origin.

Definition of the Disease

Carcinoid syndrome is a paraneoplastic endocrine syndrome typically observed in patients with neuroendocrine tumors of gastrointestinal or less frequently of bronchial origin. Several humoral factors (serotonin, histamine, kallikreins, and prostaglandins) might contribute to its pathogenesis, but the biogenic amine serotonin is the most important. Serotonin is synthesized from the amino acid tryptophan. Neuroendocrine tumors of the gastrointestinal tract are relatively rare with an incidence of about 3.5/100.000/year in studies conducted in the United States. Gastrointestinal neuroendocrine tumors can arise at many sites. Characteristic locations include the small intestine, appendix, stomach, pancreas, colon, and rectum. The incidence of lung neuroendocrine tumors varies between 0.2 and 2/100.000/year. The incidence of NET is increasing. The classification of neuroendocrine tumors has been modified extensively in the past decades. The latest World Health Organization (WHO)-based classification of gastrointestinal NET is presented in ◘ Table 44.1. Well-differentiated neuroendocrine tumors (with grades 1–2) were formerly termed carcinoid tumors as their histological morphology resembles carcinomas, but their biological behavior is much more benign. It must be stressed that even tumors with the lowest proliferation rates can metastasize. About two-thirds of the neuroendocrine tumors are not associated with clear hormonal overproduction and are thus hormonally inactive, whereas one-third are hormone-producing. Carcinoid syndrome is most often observed in tumors arising from the midgut, mostly in the small intestine, and it is typically seen in patients with multiple liver metastases. Carcinoid syndrome is the most frequent paraneoplastic endocrine syndrome in NET patients being observed in almost 20% of cases.

Pancreatic neuroendocrine tumors include hormone-producing tumors such as insulinoma (► Chap. 46), gastrinoma (► Chap. 48), and very rare tumors such as glucagonoma (incidence: 1:20 million/year), VIP-oma (incidence: 1:10 million/year), and somatostatinoma (incidence: 1:40 million/year). Glucagonoma is associated with an impaired glucose homeostasis or diabetes mellitus, and non-endocrine paraneoplastic syndromes such as migrating thrombophlebitis and a severe necrotizing skin disease, necrolytic migrating erythema (◘ Fig. 44.1). VIP-oma secretes VIP (vasoactive intestinal peptide) and is associated with severe diarrhea and hypokalemia (its alternative names include Verner–Morrison syndrome, WDHA syndrome—watery diarrhea hypokalemia achlorhydria—and pancreatic cholera). Somatostatinoma often does not have typical clinical features, but the triad of diabetes mellitus/impaired glucose homeostasis, recurrent cholelithiasis, and diarrhea or steatorrhea (fatty stool) can occur.

Case Presentation

A 60-year-old female patient was referred to our center because of flushing, abdominal pains, and diarrhea that could not be explained by routine gastroenterological examinations. Her history included appendectomy and tonsillectomy. Her current complaints started 3 years earlier. Abdominal imaging showed multiple liver lesions, the largest having a diameter of 5 cm.

What is the typical flush like in carcinoid syndrome?

The flush usually involves the upper body, and it is most commonly seen on the face. About 80–85% of patients with carcinoid syndrome have flushing. The typical flush associated with carcinoid syndrome is not accompanied by sweating (Fig. 44.2a). Emotional stress and alcohol can provoke flushes. If the carcinoid syndrome is active for a long time (usually several years), a chronic flush can develop (Fig. 44.2b). Other conditions associated with flushing are presented in Table 44.2.

What kind of other symptoms and complications might occur in carcinoid syndrome?

Secretory diarrhea is seen in about 80% of patients, and this can be very disturbing. Bronchospasm leading to dyspnea is more infrequent, observed in 10–20%.

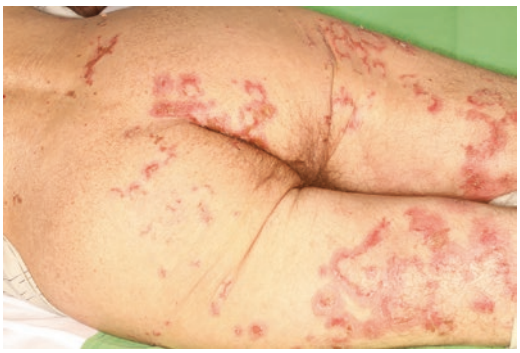

Fig. 44.1 Necrolytic migratory erythema. Necrotic, eroded, crusted and scaling, annular, red plaques on the skin of a 75-year-old male with a glucagon-producing tumor. He was first misdiagnosed as contagious impetigo in diabetes mellitus. After surgical removal of the tumor, the skin lesions healed spontaneously. (Courtesy of Prof. Miklós Sárdy, Department of Dermatology, Venereology and Dermatooncology, Semmelweis University, Budapest, Hungary)

Table 44.1 Classification of gastrointestinal neuroendocrine tumors based on the recent (2019) World Health Organization classification (WHO Classification of Tumours)

	NET-G1	NET-G2	NET-G3	NEC (small or large cell)	MINEN
Differentiation	Well-differentiated	Well-differentiated	Well-differentiated	Poorly differentiated	Well- or poorly differentiated
Grade	Low	Intermediate	High	High	Variable
Ki-67 index (%)	<3	3–20	>20	>20	Variable
Mitotic index	<2	2–20	>20	>20	Variable

Klimstra DS, Kloppel G, La Rosa S, Rindi G, Digestive system tumours, 5th ed: The WHO Classification of Tumours Editorial Board (Ed), the WHO classification of neuroendocrine neoplasms of the digestive system)
NEC neuroendocrine cancer, *MINEN* mixed neuroendocrine-non neuroendocrine neoplasm, Ki-67 is an immunostaining used to show proliferation activity, *Mitotic index* mitoses/2 mm^2, NET-G1 can be corresponded to the former term typical carcinoid, whereas NET-G2 to atypical or malignant carcinoid

Fig. 44.2 Flush in carcinoid syndrome. **a** An acute flush. **b** Chronic flush with facial venous telangiectasia

Table 44.2 Differential diagnosis of conditions associated with flushing

Physiological conditions	Diseases	Drugs
Perimenopausal syndrome Food containing capsaicin	*Neuroendocrine tumors:* pheochromocytoma, medullary thyroid cancer, VIP-oma *Hematological diseases:* systemic mastocytosis, chronic myelogenous leukemia Tumors, e.g., renal cancer Panic syndrome	Alcohol Alcohol + disulfiram Nicotinic acid Levodopa

The most frequently observed conditions are perimenopausal and panic syndromes. Pheochromocytoma is mostly associated with hypertension that is not a feature of carcinoid syndrome. Medullary thyroid cancer can secrete several different biologically active compounds resulting in flushing

A very rare phenomenon is associated to the intensive serotonin biosynthesis needing the vitamin niacin, and thus niacin deficiency can develop. Niacin deficiency can manifest itself as pellagra (a disease of 4Ds if left untreated: dermatitis, dementia, diarrhea, and death).

What is carcinoid heart disease?

Approximately 50% of patients with carcinoid syndrome suffer from carcinoid heart disease that is related to the development endocardial fibrosis mostly due to serotonin action. As serotonin is extensively metabolized by the lungs, valves of the right side of the heart are mostly involved while the left is usually spared. Tricuspid insufficiency and pulmonary stenosis can be observed. Regular (e.g., every 6 months) echocardiography is needed in patients with carcinoid syndrome.

Very rarely, retroperitoneal fibrosis can develop in severe cases of carcinoid syndrome.

What kind of other neuroendocrine neoplasms can be associated with severe diarrhea?

Besides carcinoid syndrome, severe diarrhea can also occur in pancreatic NET such as in gastrinoma (▶ Chap. 48), VIP-oma, or glucagonoma. Diarrhea might also be severe in medullary thyroid cancer, a neuroendocrine neoplasm originating from the calcitonin-producing neuroendocrine C-cells of the thyroid (▶ Chap. 19).

Which hormonal measurements should be used to confirm the diagnosis of carcinoid syndrome?

The serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) can be measured from the urine, and its significant elevation has high sensitivity and specificity. In patients with carcinoid syndrome, 5-HIAA is usually considerably elevated exceeding two or three times the upper normal reference value. Urine should be collected for 24 hours in a dark bottle in an acidic environment (similarly to urinary catecholamines, see the chapter on pheochromocytoma [▶ Chap. 37]). Several false positive and negative conditions can occur with 5-HIAA. False positive results can be seen with malabsorption and several foods (e.g., pineapple, banana, kiwi, eggplant, tomato, and nuts) containing serotonin or tryptophan. Drugs can also lead to false positive (e.g., acetaminophen, coumaric acid, and phenobarbital) or negative results (e.g., levodopa, imipramine, aspirin, and isoniazid).

The 5-HIAA measurement in this case gave 100.8 mg/24 h (normal <8.2), so it was significantly elevated.

Recently, serotonin levels can also be measured in the blood.

The other major biomarker of value in carcinoid syndrome is chromogranin A (CgA), which is a general marker of neuroendocrine tumors. In contrast with 5-HIAA, CgA is also associated with tumor burden and can be used for the follow-up of neuroendocrine tumor patients, even in patients without hormonal activity. CgA was 369.2 ng/mL (normal range: 19.4–98.1).

Which conditions could lead to false positive CgA?

CgA can be elevated in severe hypertension, pregnancy, renal insufficiency, chronic atrophic gastritis, inflammatory bowel disease, non-neuroendocrine tumors, and several other pathologies. In chronic atrophic gastritis, high gastrin stimulates CgA release. Pharmacological inhibition of gastric acid production by histamine H2 receptor-blockers and to a larger extent by proton pump inhibitors can result in sometimes significant CgA elevation, and therefore, these drugs should be omitted before CgA measurement (3 days for H2-blockers, 10–14 days for proton pump inhibitors in general). Glucocorticoids can also lead to CgA elevation.

How should we proceed?

A histological diagnosis is needed, and therefore, an ultrasound-guided liver biopsy from a metastatic lesion was performed. The liver biopsy showed a NET-G1 with a Ki-67 <1%.

Is the imaging diagnosis of liver metastases of neuroendocrine neoplasm easy?

Unfortunately, NET-metastases are often mistakenly diagnosed as hemangiomas by ultrasound, and even their computed tomography (CT) or magnetic resonance imaging (MRI) diagnosis needs expertise.

What can we infer from the histological diagnosis?

As shown in Table 44.1, this is a well-differentiated neuroendocrine tumor with a low proliferation rate. The prognosis of these tumors is good, and patients with proper treatment can survive even decades after the diagnosis. Many different treatment regimens can be tried.

Whereas the prognosis of well-differentiated NET-G1 and NET-G2 is good, neuroendocrine cancer with proliferation rates over 20% (either by Ki-67 immunostaining or by the mitotic rate) has poor prognosis. Most recently, a NET-G3 category has been established (first for pancreatic NET) that has rather high proliferation rate but shows well-differentiated morphology.

Should we look for the primary tumor?

In such patients having multiple liver metastases and carcinoid syndrome, the primary tumor is usually small and located in the small intestine. We could argue that a small tumor in comparison to the several liver metastases is of little importance, but even such small tumors can lead to intestinal obstruction. Moreover, reduction of the tumor burden (tumor debulking) in well-differentiated NET is an important treatment option, and operative procedures are thus often used in NET-G1 and NET-G2.

Which imaging techniques should be performed to find the primary tumor?

Nowadays, functional imaging based on the expression of somatostatin receptors (SSR) by NET is considered to be the most sensitive imaging modality. Neuroendocrine neoplasms express receptors for somatostatin, and marked somatostatin analogues can be used by nuclear medicine for imaging. There are five somatostatin receptors (SSR) in humans, and the somatostatin analogue used for imaging (octreotide) binds mostly receptor types

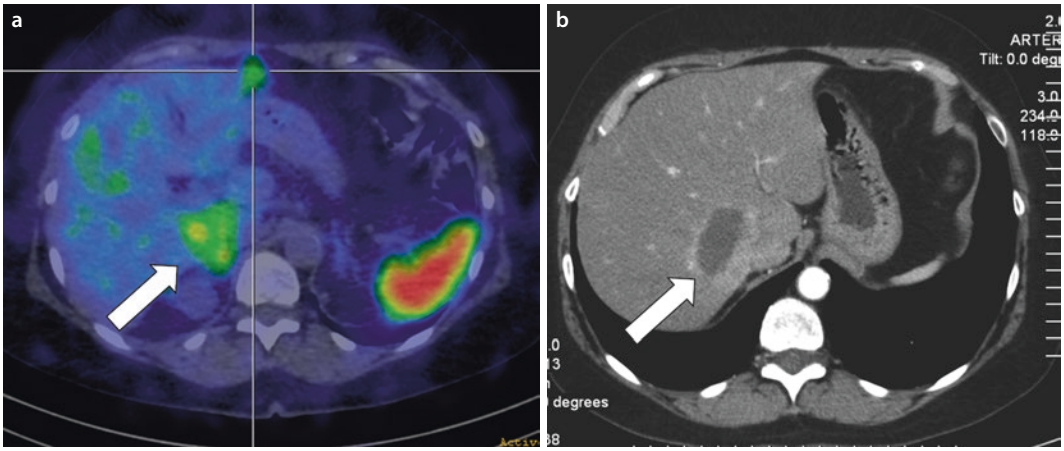

Fig. 44.3 **a** Octreotide scintigraphy SPECT-CT showing multiple metastases in the liver (green) with a large metastasis in the right lobe (arrow). **b** Necrosis in the large metastasis following TACE (transarterial chemoembolization)

2 and 5. (Native somatostatin has a very short half-life, and therefore, somatostatin analogues have been developed, e.g., octreotide and lanreotide.) Radiolabeled (^{111}In) octreotide is used in classic somatostatin receptor scintigraphy that can be combined with SPECT-CT (single photon emission computed tomography), but recently ^{68}Ga-DOTATATE PET-CT (positron emission computed tomography) with sensitivity and specificity over 90% is considered to be the most appropriate imaging.

- Ultrasound, CT, MRI, and endoscopies also belong to the standard imaging techniques of NET.

- In this case, octreotide scintigraphy was performed, which showed the SSR-positive lesions of the liver but failed to show the primary tumor (Fig. 44.3a). The primary tumor could be localized by using CT-enterography that showed the tumor in the terminal ileum.

- Laparotomy was performed and an ileal tumor with a diameter of 1 cm was removed. Histology was the same as from the liver metastasis (NET-G1, Ki-67 <1%).

? What should be the treatment strategy?

- The treatment strategy is primarily based on the pathological characteristics of the tumor. Whereas NET-G1 and NET-G2 have good prognosis and a wide array of treatment modalities are available, NEC (neuroendocrine cancer) is treated by systemic chemotherapy. General treatment options for NEN are summarized in Table 44.3.

- NET-G1 small intestinal tumors are usually slowly growing tumors, and there are reports that in hormonally inactive tumors even observation could be sufficient. However, recent findings (PROMID [octreotide] and CLARINET [lanreotide] studies) show that somatostatin analogues (SSAs) are not only useful for alleviating hormonal symptoms but also for inhibiting tumor growth. Therefore, SSAs are considered as the primary treatment option for patients with well-differentiated G1 and G2 tumors. (In G3 tumors and cancer, SSA is indicated only for alleviating hormonal symptoms.) Along with interferon-α (IFN-α), SSA therapy can be regarded as a biological treatment option for NET.

? How can somatostatin analogues be used in patients with carcinoid syndrome?

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Table 44.3 Treatment strategies for metastatic small intestinal NET based on the pathological classification

NET-G1	NET-G2	NET-G3	NEC
Tumor debulking and interventional radiological techniques (e.g., TACE and RFA)			–
SSA		PRRT[a]	Systemic chemotherapy: platinum-based (cisplatin/carboplatin) + etoposide FOLFOX FOLFIRI
PRRT		Systemic chemotherapy (FOLFOX, FOLFIRI)	
Everolimus			
IFN-α			

RFA radiofrequency ablation, *TACE* transarterial chemoembolization, *FOLFOX* Oxaliplatin-Fluorouracil-Leucovorin, *FOLFIRI* Irinotecan Fluorouracil Leucovorin
[a]If the Ki-67 index of the tumor is <50%

SSAs can alleviate symptoms associated with carcinoid syndrome in about 80% of patients. The two mainly used analogues, octreotide and lanreotide, are similarly effective, and both can be used in monthly depot injections that are very comfortable for the patient. Octreotide is also available in short-acting injections that can be used by subcutaneous or intravenous administration. In metastatic NET patients, monthly 30 mg octreotide or 120 mg lanreotide are the standard doses, but there are reports on the effectivity of even larger doses.

What is carcinoid crisis?

Carcinoid crisis is a rare condition in carcinoid syndrome patients that is most often provoked by the manipulation or treatment of the tumor (e.g., operation, interventional radiological treatment, biopsy, and peptide receptor radionuclide therapy [PRRT]). Due to excessive mediator release, significant hypotension and cardiovascular instability can occur. It should be treated with high dose intravenous octreotide (500–1000 μg) in infusion. In patients suffering from carcinoid syndrome, subcutaneous octreotide should be given before interventions (e.g., 3 × 200 μg s.c.) in addition to the depot SSA preparations to prevent carcinoid crisis.

What are the main side effects of SSAs?

As SSAs inhibit the secretion of cholecystokinin and thus gallbladder contraction, gallstones can develop in these patients. Our patient also developed gallstones and had symptoms associated with them after 5 years of SSA use and cholecystectomy had to be performed. Further side effects include diarrhea and impairment of glucose homeostasis. The most significant impairment of glucose homeostasis is seen with the most novel somatostatin analogue pasireotide that binds four somatostatin receptors (SSR1, 2, 3, and 5) and is mainly used in the treatment of acromegaly and Cushing's disease (see ▶ Chaps. 2 and 3).

What about interferon-α (IFN-α)?

IFN-α has similar efficacy as SSAs in alleviating symptoms and reducing tumor proliferation in carcinoid syndrome patients, but is much less tolerated. Major side effects of interferon therapy include flu-like symptoms (headache, muscle pains, and fever), hematologic alterations (leukopenia and anemia), and elevated transaminases. The usual dose of IFN-α in NET patients is 3 × 3 million units/week. Due to their different ways of actions, SSA and IFN-α can be combined.

We tried IFN-α in our patient and the combination with SSA was more effective than SSA alone in alleviating symptoms; moreover, both 5-HIAA excretion and CgA were reduced. However, the patient could not tolerate IFN-α, and it had to be stopped 3 months after its initiation.

If the patient still complains about diarrhea, are there further treatment options?

First, it should be examined whether it is really carcinoid syndrome that is responsible for the diarrhea. Other causes of diarrhea (e.g., dysbacteriosis, bacterial contamination, malabsorption, and pancreatic insufficiency) should be ruled out. A novel agent inhibiting tryptophan hydroxylase, telotristat, can be tried, which reduces bowel movements and can contribute to symptomatic relief in carcinoid syndrome.

What could be the next treatment step?

SSA treatment was initiated with monthly 120 mg lanreotide, but she continued to complain about diarrhea and flushing. As the tumor was progressive, we decided for a somatostatin peptide receptor radionuclide therapy.

What is PRRT (peptide receptor radionuclide therapy)?

Neuroendocrine neoplasms can be targeted by exploiting their high expression of somatostatin receptors (SSR) using radioisotopes. Radioisotope-bound SSA (mostly octreotide) is internalized by tumor cells, and the radiation kills the neighboring cells as well. Nowadays, mostly ^{177}Lutetium (^{177}Lu) is used in therapy (^{177}Lu-DOTATATE) that emits both β- and γ-radiation and is much better tolerated than the previously used ^{90}Yttrium (^{90}Y). (These radiolabeled SSA can be termed theranostics, as the same molecule can be used for diagnostic and treatment purposes.) PRRT can be used in a wide variety of NET, but the first randomized trial (NETTER-1) was performed in midgut NET.

What are the conditions needed for performing PRRT?

Patients should be in a relatively good overall condition (Karnofsky performance scale over 50), should have good renal function and blood cell counts, and should have an expected survival of at least over 3–6 months. The tumor must display higher somatostatin receptor (SSTR) expression on nuclear imaging than the liver.

What major side effects could occur related to PRRT?

Major side effects include renal, hematologic, and liver toxicity that are altogether rare. Renal toxicity was more common with ^{90}Y than with the currently used ^{177}Lu. Hematologic toxicity is a major concern. Mild forms include transient leukopenia and thrombocytopenia, but severe hematologic complications such as myelodysplastic syndrome and acute myelogenous leukemia can develop in about 1–2% of treated cases.

What kind of other treatments could be envisaged?

As shown in Table 44.3, there are still several options to be tried. Ablative treatments including interventional radiological techniques like transarterial chemoembolization (TACE) and radiofrequency ablation (RFA) are rather effective as in our patient's case shown in Fig. 44.3b displaying necrosis after TACE. Everolimus as an mammalian target of rapamycin (mTOR) inhibitor can also be tried in small intestinal NET, but it is often poorly tolerated due to many side effects including stomatitis, rash, fatigue, infections, and so on. (Everolimus and sunitinib [a tyrosine kinase inhibitor] were first shown to be effective in pancreatic NET.) These treatment options are also effective against refractory carcinoid syndrome.

Is there a role for liver transplantation for treating metastatic NET?

Very rarely, in selected cases, if the primary tumor was removed and there are no metastases outside the liver, liver transplantation can be envisaged in well-differentiated NET.

What are the treatment options for neuroendocrine carcinomas?

Neuroendocrine carcinomas (NEC) have generally poor prognosis and require systemic chemotherapy. In NEC of small intestinal origin, platinum-based chemotherapy + etoposide is the standard regimen, but other regimens (Table 44.3) can also be tried. Novel findings show that PRRT can be tried even in NEC, mostly in patients with tumors having Ki-67 index <55%. The systemic treatment of NEC of pancreatic origin includes streptozotocin + 5-fluorouracil, but the oral capecitabine/temozolomide combination (CAPTEM) is also increasingly used.

Epilogue

Our patient is in a relatively good overall condition after more than 10 years of treatment. The management of neuroendocrine neoplasms necessitates a multidisciplinary approach involving pathology, endocrinology, gastroenterology, surgery, oncology, nuclear medicine, and radiology. Patients should be treated by centers having expertise in the management of this disease.

Tips

- The reader is advised to read the next chapter presenting a bronchial neuroendocrine tumor associated with an ectopic ACTH syndrome (▶ Chap. 45) and the chapters dealing with pancreatic neuroendocrine tumors (insulinoma [▶ Chap. 46] and gastrinoma [▶ Chap. 48]).

Take Home Messages

- Carcinoid syndrome is a rare paraneoplastic syndrome associated with hormonally active neuroendocrine neoplasms (NETs), most frequently observed in patients with small intestinal NET giving multiple liver metastases.
- NETs have different histological subtypes that are very important to know for planning treatment.
- Useful biomarkers for diagnosis include 5-hydroxyindoleacetic acid (5-HIAA), a serotonin metabolite, and chromogranin A as a general NET-marker.
- High expression of somatostatin receptors by NET is exploited in both the diagnosis and the treatment.
- Somatostatin analogues are efficient in reducing hormonal symptoms, and these have also antitumoral activity.
- Radiolabeled somatostatin analogues can be used for diagnosis by nuclear medicine and also for treatment (peptide receptor radionuclide treatment) (theranostics).
- In well-differentiated small intestinal neuroendocrine tumors (grades 1 and 2), other treatment modalities include surgery (debulking), ablative interventional radiological treatments (e.g., transarterial chemoembolization and radiofrequency ablation), and targeted treatment (everolimus).
- Poorly differentiated small intestinal neuroendocrine cancer (grade 3) should be treated with systemic chemotherapy.

Suggested Reading

1. Caplin ME, Pavel M, Cwikla JB, Phan AT, Raderer M, Sedlackova E, Cadiot G, Wolin EM, Capdevila J, Wall L, Rindi G, Langley A, Martinez S, Blumberg J, Ruszniewski P. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014;371(3):224–33. https://doi.org/10.1056/NEJMoa1316158.

2. Caplin ME, Baudin E, Ferolla P, Filosso P, Garcia-Yuste M, Lim E, Oberg K, Pelosi G, Perren A, Rossi RE, Travis WD, ENETS consensus conference participants. Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids. Ann Oncol. 2015;26(8):1604–20. https://doi.org/10.1093/annonc/mdv041.
3. Clift AK, Kidd M, Bodei L, Toumpanakis C, Baum RP, Oberg K, Modlin I, Frilling A. Neuroendocrine neoplasms of the small bowel and pancreas. Neuroendocrinology. 2019;110:444. https://doi.org/10.1159/000503721.
4. Halperin DM, Shen C, Dasari A, Xu Y, Chu Y, Zhou S, Shih YT, Yao JC. Frequency of carcinoid syndrome at neuroendocrine tumour diagnosis: a population-based study. Lancet Oncol. 2017;18(4):525–34. https://doi.org/10.1016/S1470-2045(17)30110-9.
5. Hassan SA, Palaskas NL, Agha AM, Iliescu C, Lopez-Mattei J, Chen C, Zheng H, Yusuf SW. Carcinoid heart disease: a comprehensive review. Curr Cardiol Rep. 2019;21(11):140. https://doi.org/10.1007/s11886-019-1207-8.
6. Klimstra DS. Pathologic classification of neuroendocrine neoplasms. Hematol Oncol Clin North Am. 2016;30(1):1–19. https://doi.org/10.1016/j.hoc.2015.08.005.
7. Lawrence B, Gustafsson BI, Chan A, Svejda B, Kidd M, Modlin IM. The epidemiology of gastroenteropancreatic neuroendocrine tumors. Endocrinol Metab Clin North Am. 2011;40(1):1–18; vii. https://doi.org/10.1016/j.ecl.2010.12.005.
8. Niederle B, Pape UF, Costa F, Gross D, Kelestimur F, Knigge U, Oberg K, Pavel M, Perren A, Toumpanakis C, O'Connor J, O'Toole D, Krenning E, Reed N, Kianmanesh R. ENETS consensus guidelines update for neuroendocrine neoplasms of the jejunum and ileum. Neuroendocrinology. 2016;103(2):125–38. https://doi.org/10.1159/000443170.
9. Oberg K. Medical therapy of gastrointestinal neuroendocrine tumors. Visc Med. 2017;33(5):352–6. https://doi.org/10.1159/000475831.
10. Oberg K. The genesis of the neuroendocrine tumors concept: from Oberndorfer to 2018. Endocrinol Metab Clin N Am. 2018;47(3):711–31. https://doi.org/10.1016/j.ecl.2018.05.003.
11. Rindi G, Klimstra DS, Abedi-Ardekani B, Asa SL, Bosman FT, Brambilla E, Busam KJ, de Krijger RR, Dietel M, El-Naggar AK, Fernandez-Cuesta L, Kloppel G, McCluggage WG, Moch H, Ohgaki H, Rakha EA, Reed NS, Rous BA, Sasano H, Scarpa A, Scoazec JY, Travis WD, Tallini G, Trouillas J, van Krieken JH, Cree IA. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. Mod Pathol. 2018;31(12):1770–86. https://doi.org/10.1038/s41379-018-0110-y.
12. Rinke A, Muller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, Mayer C, Aminossadati B, Pape UF, Blaker M, Harder J, Arnold C, Gress T, Arnold R. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID study group. J Clin Oncol. 2009;27(28):4656–63. https://doi.org/10.1200/jco.2009.22.8510.
13. Singh S, Carnaghi C, Buzzoni R, Pommier RF, Raderer M, Tomasek J, Lahner H, Valle JW, Voi M, Bubuteishvili-Pacaud L, Lincy J, Wolin E, Okita N, Libutti SK, Oh DY, Kulke M, Strosberg J, Yao JC, Pavel ME, Fazio N. Everolimus in neuroendocrine tumors of the gastrointestinal tract and unknown primary. Neuroendocrinology. 2018;106(3):211–20. https://doi.org/10.1159/000477585.
14. Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, Mittra E, Kunz PL, Kulke MH, Jacene H, Bushnell D, O'Dorisio TM, Baum RP, Kulkarni HR, Caplin M, Lebtahi R, Hobday T, Delpassand E, Van Cutsem E, Benson A, Srirajaskanthan R, Pavel M, Mora J, Berlin J, Grande E, Reed N, Seregni E, Oberg K, Lopera Sierra M, Santoro P, Thevenet T, Erion JL, Ruszniewski P, Kwekkeboom D, Krenning E. Phase 3 trial of (177)Lu-Dotatate for Midgut neuroendocrine tumors. N Engl J Med. 2017;376(2):125–35. https://doi.org/10.1056/NEJMoa1607427.

Ectopic ACTH Syndrome Caused by a Bronchial Neuroendocrine Tumor

Géza Nagy

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_45

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Opening

In this chapter, the clinical aspects of Cushing's syndrome caused by an ectopic adrenocorticotropic hormone (ACTH)-secreting tumor will be discussed. Following the course of a patient eventually diagnosed with an ACTH-producing atypical neuroendocrine tumor (NET; carcinoid) in the lung, the clinical features, diagnosis, and treatment of ectopic ACTH syndrome will be presented.

Definition of the Disease

Ectopic adrenocorticotropic hormone syndrome is defined as an endogenous Cushing's syndrome caused by a histologically heterogeneous group of ACTH-secreting neuroendocrine neoplasms (NEN or NET, neuroendocrine tumor). The syndrome belongs to the group of paraneoplastic endocrine syndromes. In exceptionally rare cases, lymphomas or sarcomas have also been shown to be the source of ectopic ACTH production.

The primary tumor may arise from a wide variety of organs, but most commonly in the lung (i.e., small cell lung cancer [SCLC]), pancreas, and thymus.

What feature of this case raises the suspicion of ectopic ACTH syndrome?

The patient had severe life-threatening hypokalemia; however, she had no apparent cause of this electrolyte imbalance. She was not taking diuretics or any other medications. There was a complete absence of gastrointestinal symptoms and signs of kidney disorder. On the other hand, an extraordinarily high potassium dose was needed. These findings pointed to the likelihood of the presence of either primary aldosteronism (see in ▶ Chap. 28.) or other hormone excess with mineralocorticoid activity. ◘ Table 45.1 summarizes the major causes of hypokalemia.

Is the clinical picture of ectopic ACTH syndrome different from the classical Cushing's phenotype?

The classical phenotype in Cushing's syndrome is presented in the chapters on pituitary Cushing's disease (▶ Chap. 3) and adrenal Cushing's syndrome (▶ Chap. 28). The classical phenotype includes centripetal obesity, striae, buffalo hump, moon-like face, and so on. In ectopic ACTH syndrome associated Cushing's

Case Presentation

A 60-year-old postmenopausal female patient presented herself at our department in an emergency setting. Her main complaints started a few days ago and included severe general weakness and symmetrical swelling of both lower extremities. She had no relevant previous medical history and did not take any medications regularly.

Besides apparent symmetric edemas on both legs, no abnormalities have been found on a physical examination. Her blood pressure was normal. There were no signs of kidney or liver failure. Her blood glucose values showed a prediabetic state in her carbohydrate metabolism. The cause of her symptoms was soon unveiled by a routine lab evaluation showing severe hypokalemia (serum potassium 1.6 mmol/L, normal: 3.5–5.0). Interestingly, she had no signs of arrhythmias or any other ECG abnormalities. Urgent supplementation of intravenous and oral potassium chloride has been commenced. In an effort to reach physiologic serum potassium levels, it has been established that extraordinarily high dose (20 g/day) of replacement therapy was required to reach normokalemia.

Table 45.1 Major causes of hypokalemia

Decreased intake of potassium
Potassium shift into cells
Alkalosis
Hyperinsulinemia
Hypothermia
Drugs (beta receptor agonists, chloroquine)
Gastrointestinal loss of potassium
Vomiting
Diarrhea
Urinary loss of potassium
Diuretics
Polyuria
Mineralocorticoid excess[a]
Severe hypercortisolism
Renal tubular acidosis
Salt-wasting nephropathies
Hypomagnesemia
Increased loss with perspiration

[a]Mineralocorticoid excess includes several diseases such as primary aldosteronism (► Chap. 28), secondary aldosteronism (► Chap. 29), forms of congenital adrenal hyperplasia associated with hypertension and hypokalemia (e.g., 11β-hydroxylase deficiency or 17α-hydroxylase/17,20-lyase deficiency [► Chap. 35]) or apparent mineralocorticoid excess (► Chap. 35)

syndrome, however, these typical phenotypic signs are often lacking, as the syndrome is progressing rapidly and there is not enough time for the development of these symptoms. Severe and rapidly progressing diabetes mellitus, muscle weakness, hypertension, and hypokalemia can be the presenting signs. Hypokalemia is due to the excessive levels of cortisol. The HSD11B2 enzyme (11ß-hydroxysteroid dehydrogenase 2) defends the mineralocorticoid (aldosterone) receptor from the more abundant cortisol by metabolizing it to inactive cortisone in aldosterone-responsive organs. In conditions of excessive cortisol production (e.g., ectopic ACTH syndrome or adrenocortical cancer), the capacity of the enzyme is being exhausted and cortisol binds with high affinity to the mineralocorticoid receptor. If ACTH levels are high, even hyperpigmentation can occur.

What tests should be done to assess the endocrine origin of hypokalemia?

After correcting the electrolyte imbalance, it was key to evaluate the presence of primary aldosteronism (see also in ► Chap. 29.). Even though the patient was lacking the typical signs of Cushing's syndrome, the possibility of hypercortisolism had also to be investigated (see in ► Chaps. 3 and 27).

Case Presentation Continued

Table 45.2 shows the hormonal results of the patient.

Primary aldosteronism was ruled out (normal aldosterone) on one hand. On the other hand, the patient has severe ACTH-dependent Cushing's disease (elevated late-night cortisol values and 24-hour urinary free cortisol [UFC], no suppression on low-dose dexamethasone test, and ACTH is elevated), which is most possibly causing her symptoms. (Suppressed renin is due to the mineralocorticoid activity of excessive glucocorticoid production.)

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Table 45.2 Hormone results showing ACTH-dependent hypercortisolism

Hormone test	Result	Reference range
Plasma renin activity	<0.1 ng/mL/h	0.17–2.01
Plasma aldosterone	0.8 ng/dL	0.7–15.0
Morning serum cortisol	*831 nmol/L*	220–690
Late-night serum cortisol	*917.8 nmol/L*	<136
Late-night salivary cortisol	*232.1 nmol/L*	<11.9
24-hour urinary free cortisol (UFC)	*7206 nmol/day*	100–379 nmol/day
Low-dose dexamethasone suppression test	*948.7 nmol/L*	<50
ACTH	132 pg/mL	5–60

What might be the main causes of ACTH-dependent Cushing's syndrome?

Overall, there are three main causes of ACTH-dependent Cushing's syndrome. The vast majority of the cases are caused by Cushing's disease, in which the source of the excess ACTH secretion originates from the pituitary gland. In ectopic ACTH syndrome, ACTH secretion of a non-pituitary tumor is the cause of hypercortisolism. And finally, in exceptionally rare cases (less than 1%), an ectopic corticotropin-releasing hormone (CRH)-secreting tumor may be the cause of Cushing's syndrome.

Are there any further tests needed to evaluate the cause of Cushing's syndrome?

Yes, since the treatment options and prognosis of all entities are different, a precise diagnosis is mandatory to plan treatment. Even though—just like in the presented case—glucocorticoid overproduction is usually much more severe, and the presence of hypokalemia is much more common in ectopic ACTH syndrome compared to Cushing's disease, additional tests are needed to differentiate between these two distinct entities. These tests include noninvasive and invasive venous sampling and imaging studies.

Non-invasive tests:

The CRH stimulation test

The physiologic response to IV-administered CRH is a 35–900% increase in serum ACTH and a 20–600% increase in serum cortisol within 120 minutes. As opposite to normal individuals and Cushing's disease patients, patients with ectopic ACTH syndrome do not respond to exogenous CRH stimulation. This is due to suppression of pituitary ACTH stimulation seen in these patients. The test is done in a supine position after a few hours of fasting. And 1 μg of synthetic corticotropin-releasing hormone is administered intravenously. Blood sampling for serum cortisol and ACTH is done from a peripheral vein in every 15 minutes for 60 minutes and at 90 and 120 minutes.

The high-dose dexamethasone suppression test

Since ectopic ACTH-producing tumors are completely resistant to the cortisol-induced feedback mechanism as opposite to the only relative resistance seen in ACTH-producing pituitary adenomas, the high-dose dexamethasone may also be a useful tool in differentiating between the causes of hypercortisolism. In its overnight form, the test is carried out by administering 8 mg of dexamethasone orally at

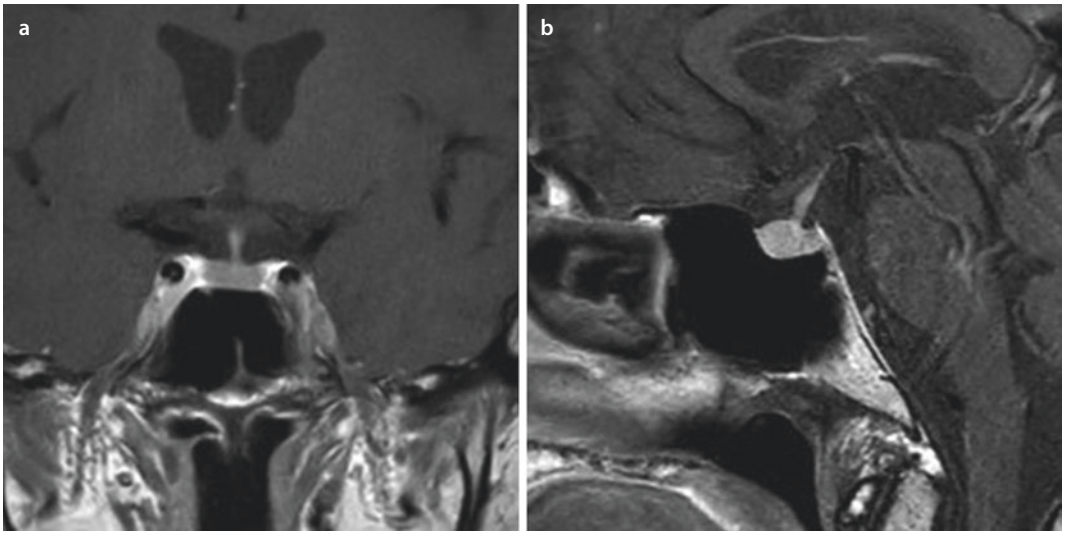

Fig. 45.1 Coronal **a** and sagittal **b** cross-section of a normal sella MRI showing no signs of a micro- or macroadenoma

23:00 and peripheral venous blood sampling the following morning cortisol levels. Non-suppressed morning cortisol (>140 nmol/L) values indicate ectopic ACTH-secreting malignant tumor.

- Despite being easy and safe to perform these noninvasive tests, alone they are neither sensitive nor specific enough to categorize every patient precisely. Thus, both tests should be performed, and the results are required to be unanimous and supported with imaging studies. Otherwise, invasive testing is indicated.

- *Imaging*:

- A native and gadolinium contrast-enhanced MRI of the pituitary gland is the best choice for visualizing an ACTH-producing adenoma in the sellar region.

- In the present case, a pituitary magnetic resonance imaging (MRI) (see Fig. 45.1) has been performed to assess the cause of Cushing's syndrome. The sella MRI showed no visible adenoma in the pituitary, which strengthened the likelihood of ectopic ACTH syndrome and was necessary to do before performing invasive sampling.

- *Invasive testing*:

- Bilateral inferior petrosal sinus sampling (BIPSS) is the gold standard test to demonstrate pituitary ACTH hypersecretion and to rule out or prove ectopic ACTH secretion. The test is performed after cannulation of both inferior petrosal sinus (IPS) via the femoral or jugular veins. During the test, bilateral central and unilateral peripheral serum ACTH is measured before and after administration of CRH. In case of a central-to-peripheral plasma ACTH gradient of <2.0 before CRH administration or <3.0 after CRH is diagnostic of an ectopic source of ACTH. (Vice versa, ACTH gradients over 2.0 and 3.0 before and after CRH, respectively, are characteristic for a pituitary ACTH source.)

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Case Presentation Continued

In the present case, in view of a negative pituitary MRI and due to the high likelihood of ectopic ACTH syndrome based on the clinical setting, BIPSS has been performed. The results (presented in Table 45.3) show a low central to peripheral ratio on both basal and CRH-stimulated ACTH levels confirming an ectopic ACTH syndrome.

Table 45.3 Results of BIPSS

	Peripheral ACTH	Left IPS ACTH	Right IPS ACTH	IPS: peripherals ratio
Basal	117 pg/mL	135 pg/mL	134 pg/mL	135/117 = 1.15
5-minute post CRH	118 pg/mL	133 pg/mL	140 pg/mL	140/118 = 1.18
10-minute post CRH	110 pg/mL	121 pg/mL	131 pg/mL	
15-minute post CRH	135 pg/mL	135 pg/mL	139 pg/mL	

How to find the ACTH-secreting tumor?

One of the most difficult challenges in managing patients with ectopic ACTH syndrome is to localize the primary tumor.

Unfortunately, there is no clear guidance yet on which radiological method is best suited for locating the neoplasm. Most tumors associated with ectopic ACTH syndrome reside in the thorax. Contrast-enhanced computed tomography (CT) of the thorax seems to be the best modality based on common etiology. Abdominal CT or MRI can be a sensitive method to assess distant metastasizes. Also, nuclear imaging, such as ^{18}F-fluorodeoxyglucose (FDG)-PET-CT and ^{111}In-octreotide scintigraphy or ^{68}Ga-DOTATATE-PET-CT, may be helpful in tumor detection in poorly or well-differentiated neuroendocrine neoplasms, respectively.

In the present case, a contrast-enhanced thoraco-abdomino-pelvical CT scan has been performed. The images have revealed a small mass of about 30 × 12 mm in size surrounding the bronchi in the eighth segment of the right lung (see Fig. 45.2). Additionally, an about 20 mm large solitary bone metastasis has been found in the fourth rib on the right side. The abdominal CT has also revealed adrenal glands showing signs of adrenal hyperplasia (Fig. 45.2). This was most likely caused by the constant adrenal stimulation caused by the ectopic ACTH.

Should histological sampling be performed in lung neuroendocrine tumors?

Neuroendocrine tumors of the lung include a diverse spectrum of neoplasms showing differences in differentiation and mitotic activity. Different pulmonary NETs require different therapy and have different overall prognosis. Thus, it is of great importance to perform histologic analysis of the tumor.

What are the differences among bronchial NETs?

Neuroendocrine tumors of the lung may be well-differentiated, also known as pulmonary carcinoids (PCs). PCs may be low-grade, also called typical carcinoids (TCs), or intermediate-grade, also known as atypical carcinoids (ACs). (The term carcinoid is still in use with bronchial neu-

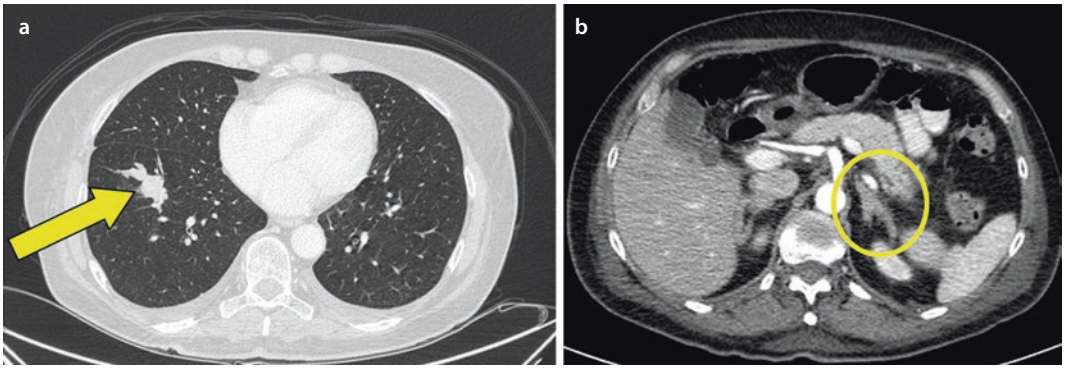

Fig. 45.2 Ectopic ACTH-secreting bronchial tumor in S8 of the right lung **a** and hyperplastic adrenal gland **b**

roendocrine neoplasms.) While TCs grow slowly and rarely give distant metastasizes and have a better prognosis, ACs have a higher likelihood of recurrence, grow faster, are prone to give distant metastases, and have a worse prognosis. PCs are rare and account for about 1–2% of all lung malignancies in adults. TCs are eight to ten times more common compared to ACs, making ACs the most uncommon of lung NETs. On the other end of the spectrum are poorly differentiated neuroendocrine carcinomas such as small cell lung cancer and large cell neuroendocrine cancer (LCNEC), both of which generally grow very rapidly and, because of their potential to give distant metastases, have a poor prognosis.

Case Presentation Continued

In the present case, due to its peripheral localization, the tumor was inaccessible via bronchoscopy. Thus, CT-guided biopsy has been performed. The histological evaluation of the samples revealed a tumor with cytologically bland immature cells, containing regular round nuclei with finely dispersed chromatin and inconspicuous small nucleoli arranged in distinct organoid growth patterns with a delicate vascular stroma. Within the tumor, dot-like necrosis was visible. Immunohistochemical (IH) staining showed positivity for thyroid transcription factor (TTF-1), cytokeratin (CK8-18), CD56, chromogranin A (CgA), synaptophysin, and ACTH. The mitotic activity of the tumor cells was approximately 10–15%. Based on these findings, the diagnosis of an atypical bronchial carcinoid was made (see Fig. 45.3).

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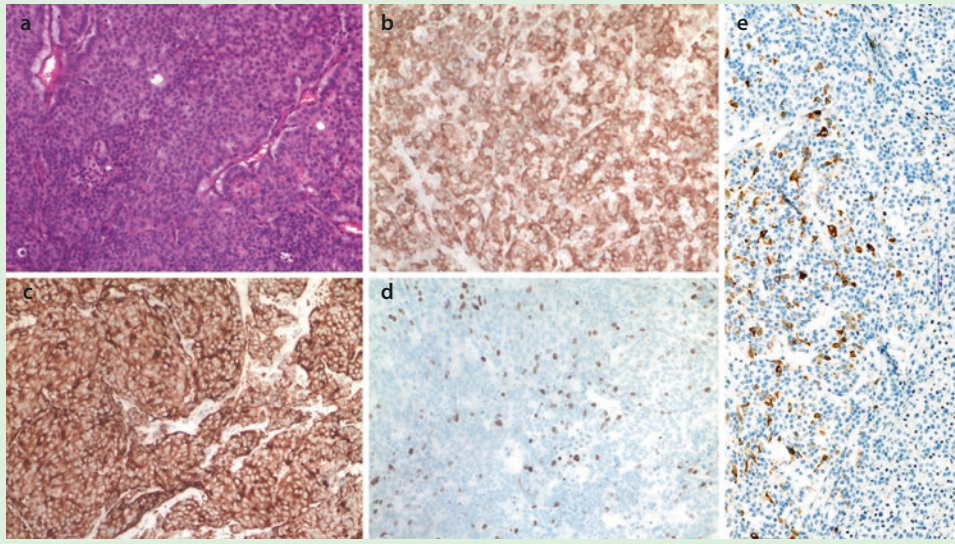

Fig. 45.3 Histological pictures of an atypical bronchial carcinoid, 20x magnification. **a** Hematoxylin-eosin staining. **b** Synaptophysin immunohistochemistry. **c** Chromogranin A immunohistochemistry. **d** ACTH immunohistochemistry. **e** Ki-67 immunohistochemistry. (Courtesy of Katalin Borka MD PhD [2nd Department of Pathology, Semmelweis University], and János Szőke MD PhD [National Institute of Oncology])

Do all lung NET-s produce ACTH?

No. In fact, most of them do not. The most common paraneoplastic endocrine syndrome in PCs is the carcinoid syndrome (▶ Chap. 45) found in about 2–5% of well-differentiated tumor cases. The second most frequent functioning syndrome is Cushing's syndrome. It is worth noting here that the carcinoid syndrome associated with pulmonary carcinoids can be different from the classical carcinoid syndrome, the so-called lung NET-variant or atypical carcinoid syndrome. In this variant form, flushes can last for hours or even days, and various symptoms such as anxiety, disorientation, hypersalivation, hypotension, and tachycardia can be observed. Histamine may play a major role in this variant. Carcinoid crisis (▶ Chap. 44) is very rare in patients with PCs.

In rare and extremely rare cases, acromegaly and ectopic insulin secretion has also seen in PCs. It is also worth mentioning that the syndrome of inappropriate antidiuretic hormone secretion (SIADH) is seen in 5% in SCLC cases but rarely in PC (for further reading, see ▶ Chap. 10).

Are there any curative treatment options in this patient's case?

The only curative treatment option that might free the patient of the malignant tumor as well as put an end to the ectopic ACTH production is surgical. Imaging studies suggested that the primary tumor in S8 of the right lung could be removed by lobectomy and lymph node dissection along with the solitary bone metastasis.

What needs to be done prior to surgery?

In this patient's case, Cushing's syndrome was severe, highlighted by the more than ten times upper normal limit 24-hour urinary cortisol excretions. Thus, prior to surgery, the symptoms of hypercortisolism should be alleviated to avoid pre and post-

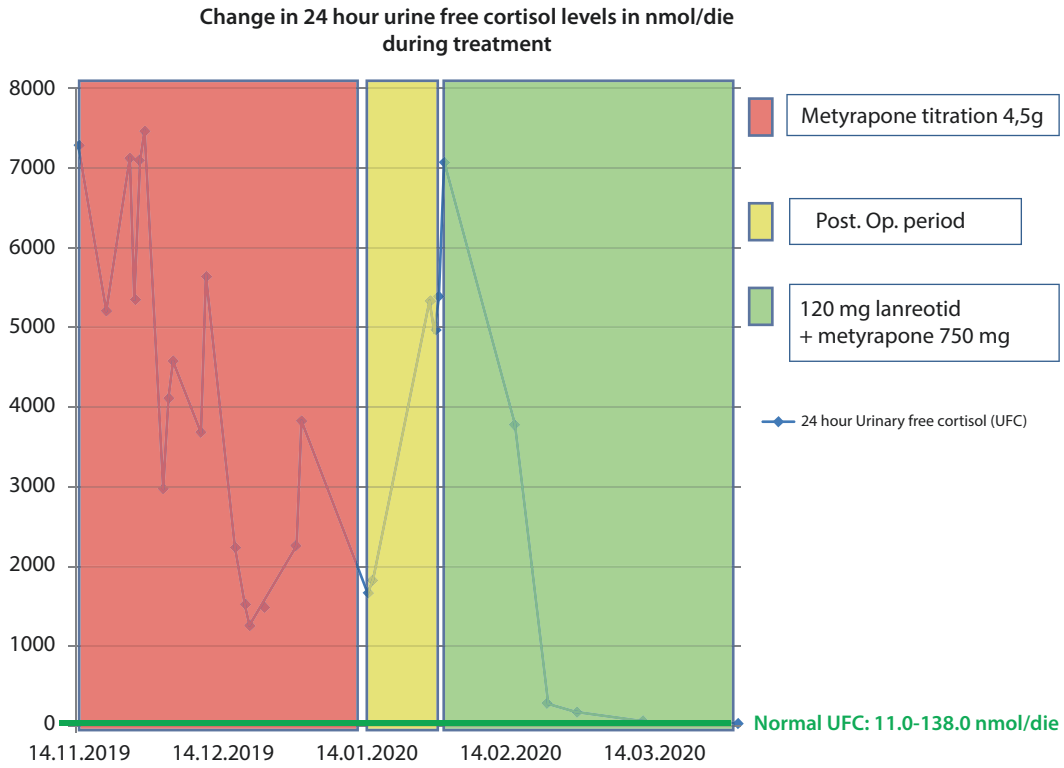

Fig. 45.4 Overall change of UFC levels in the presented case during the different treatment periods. Note: The rise of UFC in the postoperative period is due to the discontinuation of metyrapone therapy

operative complications such as impaired wound healing, infections, thrombosis, and arrhythmias due to severe hypokalemia. Thus, steroid biosynthesis inhibitors should be introduced. Preoperative medical therapeutic options included ketoconazole, metyrapone, intravenous etomidate, or the glucocorticoid receptor antagonist mifepristone. Ketoconazole, given at a daily dose of 600–800 mg, is the most commonly used and effective. Metyrapone is also often used in this setting, and therapy starts at 1 g/day divided into four doses and increased to a maximum dose of 6 g/day. Anticoagulant therapy should also be started with low molecular weight heparin.

In the present case, the patient was started on metyrapone and titrated up to a dose of 4.5 g/day. Despite steroid biosynthesis inhibition, eucortisolemia could not be reached (see Fig. 45.4), and the patient required oral potassium supplementation and potassium-sparing diuretics to fully correct serum potassium levels.

How can the success of surgery be evaluated?

Histological examination of the removed specimens, tumor markers, such as chromogranin A (CgA), or neuron-specific enolase (NSE) and re-evaluation of the patient for ectopic ACTH syndrome are the key components of evaluating surgical success. A total resection, normalized serum tumor markers (if these were elevated before surgery), and complete remission of hormonal symptoms suggest surgical success.

Unfortunately, in the present case, despite both tumors seeming to be macroscopically removed during the surgical process, histology indicated that the cortical layer

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of the removed rib was infiltrated by tumor cells and local soft tissue invasion was present confirming R1 resection. These findings were also confirmed by persistent ectopic ACTH syndrome during the postoperative period (see Fig. 45.4). It is worth mentioning that even though the procedure did not turn out to be curative, the debulking of most of the tumor made eucortisolemia achievable with metyrapone.

In case of the residual atypical carcinoid and persistent ectopic ACTH-dependent syndrome, what treatment options are available for hormone control?

Cushing's syndrome can be treated with previously mentioned steroid biosynthesis inhibitors as well as somatostatin analogues (SSA). If hormonal control cannot be achieved via medical therapy, other more invasive anti-tumor therapy such as metastasis resection, radiofrequency ablation, arterial chemoembolization, or in uncontrollable cases bilateral adrenalectomy should be considered.

What treatment options are there to control tumor growth or induce regression?

In asymptomatic patients with slowly growing low tumor burden, options include only observation, as well. In patients in need of tumor stabilization, SSA treatment may be an option due to the expression of somatostatin receptors by the tumor. In progressive, well-differentiated PCs expressing somatostatin receptors, systemic peptide receptor radionuclide therapy (PRRT) with ^{90}Yttrium-DOTA octreotide or ^{177}Lutetium DOTA octreotide may also be effective. Side effects of PRRT include hematological toxicities and renal toxicity (▶ Chap. 45). Advanced well-differentiated intermediate-grade PCs not expressing somatostatin receptors should be treated with everolimus, a mammalian target of rapamycin (mTOR) inhibitor, or anti-angiogenetic agents such as pazopanib. And finally, in advanced intermediate-grade lung ACs, systemic chemotherapy with 5-fluorouracil (5-FU) and temozolomide-based chemotherapy can be advised. Etoposide and cisplatin combination due to its high toxicity is preserved for high-grade lung neuroendocrine cancer such as SCLC.

Case Presentation Continued

In the present case, even though tumor burden was undetectable, the patient had persistent hypercortisolism caused by an intermediate-grade AC. Thus, on the top of steroid biosynthesis inhibitor metyrapone, SSA has been started to inhibit tumor cell growth. As presented in Fig. 45.4, eucortisolemia could be reached using this combination therapy. On follow-up imaging, we have seen no signs of relapse either.

Is routine genetic testing necessary in patients with PC?

No. PCs are rarely (<5%) associated with multiple endocrine neoplasia type 1 (MEN1). Clinical assessment such as family history and screening routine lab tests such as serum calcium, parathyroid hormone, and prolactin is sufficient to follow up and select patient who should be tested for MEN1.

Tips

The reader is advised to read (or repeat) the chapters on Adrenal Cushing's syndrome (▶ Chap. 27) and pituitary Cushing's disease (▶ Chap. 3). Moreover, the previous chapter on a small intestinal neuroendocrine tumor with carcinoid syndrome is interesting to read, and this includes more pieces of information on somatostatin analogues and peptide receptor radionuclide treatment (▶ Chap. 44). The syndrome of inappropriate secretion of antidiuretic hormone is discussed in ▶ Chap. 10.

Take Home Messages

- Ectopic ACTH syndrome is caused by malignant ACTH-producing non-pituitary tumors, most commonly in the lungs, thymus, and pancreas.
- The clinical picture is markedly different compared to other causes of Cushing's syndrome, as patients usually lack the typical symptoms of Cushing's disease.
- Ectopic ACTH syndrome is associated with elevated ACTH levels and usually markedly elevated cortisol levels.
- Ectopic ACTH syndrome is associated with severe, commonly life-threatening hypercortisolism complicated with severe hypokalemia, serious infections, thromboembolism, and impaired wound healing.
- Imaging needed to locate the tumor includes CT, MRI, FDG-PET-CT, and Octreoscan.
- The only curative option is surgery.
- Palliative treatment options include steroid biosynthesis inhibitors and depending on the grade anti-cancer therapy (somatostatin analogues, interferon, mTOR inhibitors, PRRT, or systemic chemotherapy).

Suggested Reading

1. Caplin ME, Baudin E, Ferolla P, Filosso P, Garcia-Yuste M, Lim E. Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids. Ann Oncol. 2015;26(8):1604–20. https://doi.org/10.1093/annonc/mdv041.
2. Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, Yao JC. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol. 2017;3(10):1335–42. https://doi.org/10.1001/jamaoncol.2017.0589.
3. de Herder WW, Lamberts SW. Tumor localization--the ectopic ACTH syndrome. J Clin Endocrinol Metab. 1999;84(4):1184–5. https://doi.org/10.1210/jcem.84.4.5690.
4. Igaz P, Tombol Z, Szabo PM, Liko I, Racz K. Steroid biosynthesis inhibitors in the therapy of hypercortisolism: theory and practice. Curr Med Chem. 2008;15(26):2734–47. https://doi.org/10.2174/092986708786242921.
5. Loriaux DL. Diagnosis and differential diagnosis of Cushing's syndrome. N Engl J Med. 2017;376(15):1451–9. https://doi.org/10.1056/NEJMra1505550.
6. Nieman LK. Diagnosis of Cushing's syndrome in the modern era. Endocrinol Metab Clin North Am. 2018;47(2):259–73. https://doi.org/10.1016/j.ecl.2018.02.001.
7. Nieman LK, Biller BM, Findling JW, Murad MH, Newell-Price J, Savage MO, Endocrine S. Treatment of Cushing's syndrome: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2015;100(8):2807–31. https://doi.org/10.1210/jc.2015-1818.

Insulinoma

Gerlies Treiber and Peter Igaz

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_46

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Opening

In this chapter, the reader will get acquainted with the clinical features, diagnosis, and treatment of endogenous hyperinsulinism caused by insulinoma. Insulinoma belongs to the group of duodenopancreatic neuroendocrine tumors. A major differential diagnostic problem related to exogenous, factitious hypoglycemia is presented in the following chapter.

Definition of the Disease

Insulinoma is a mostly benign, rare neuroendocrine tumor with an incidence of about 4/million/year. The autonomous insulin production by the tumor leads to spontaneous hypoglycemia that results in two major groups of symptoms: neuroglycopenia and adrenergic symptoms. Due to the anabolic effects of insulin and the exaggerated food consumption to avoid recurring hypoglycemia, patients can experience significant weight gain as well. Despite being mostly a histologically benign tumor, it is associated with significant morbidity and mortality.

Case Presentation

A 30-year-old man was admitted to the hospital because of daily episodes of altered mental status during a gastrointestinal infection. The patient had been well until 2 years before admission, when he noticed episodes with numbness of his mouth, dizziness, blurry vision, and mental blackouts. His family members observed altered childlike behavior and disturbed speech. The patient returned to his normal mental status initially after 10 minutes. He was not able to recall the details of these episodes. Six months before admission, the frequency and duration of the episodes increased. Symptoms appeared before meals and at night ceased after intake of carbs or sugar. He gained 7 kg within the last 6 months. He did seek medical care with a neurologic work-up and symptoms were first attributed to panic attacks. The patient took no medication except Trazodone (antidepressant) at night since 2 months. He did not use any illicit drugs or anabolics. He admitted the intake of several protein preparations during his 15 years of bodybuilding training.

There was no family history of pancreatic or autoimmune disease, and no one in the patient's home used insulin or other diabetes medication. At admission, his blood glucose level was 27 mg/dL (1.5 mmol/L), the weight was 104 kg, and the BMI 32.5 kg/m^2.

What would be the most likely diagnosis?

The symptoms of the patient raise the suspicion for neuroglycopenia that is alleviated by glucose administration. Moreover, the documented low blood glucose confirms hypoglycemia. The patient should be examined for organic hypoglycemia, and thus, insulinoma is the most probable diagnosis. Weight gain is also typical in insulinoma patients, which is due to the anabolic effects of insulin and the necessity of frequent eating to avoid hypoglycemia.

What is Whipple's triad?

Whipple's triad comprises clinical symptoms of hypoglycemia, documented hypoglycemia (serum glucose <3 mmol/L

or 55 mg/dL), and the rapid amelioration of symptoms following glucose administration.

What could be proposed as the most important clinical test to confirm the suspicion of insulinoma?

The 72-hour fast test is the gold standard. About 90% of insulinoma patients present hypoglycemia within 48 hours of the test.

How should the 72-hour fast test be performed?

The in-patient does not receive any food for 72 hours but can drink water without limitation. Blood is taken regularly for serum glucose, insulin, and C-peptide measurements. If blood glucose reaches 3.3 mmol/L (60 mg/dL), blood should be taken every 2 hours onward. Blood should be taken if the patient experiences symptoms of hypoglycemia. The test is usually terminated if the patient presents clear symptoms of hypoglycemia that is mostly judged by cognitive functions (e.g., by counting). For a successful test, documented hypoglycemia is needed: serum glucose <3 mmol/L or 55 mg/dL (previously the limit was <2.2 mmol/L [40 mg/dL]). Plasma insulin is usually higher than 3 μIU/mL (20.8 pmol/L) at a blood glucose lower than 3 mmol/L in patients with insulinoma. Once the fast is concluded, 1 mg of glucagon can be given intravenously and plasma glucose is then measured at 10, 20, and 30 minutes after injection. The results of the fasting test for the patient along with differential diagnostic issues are presented in ◘ Table 46.1.

What should be determined from the blood samples?

Parallel measurement of insulin and C-peptide are mandatory, but if available, proinsulin and β-hydroxybutyrate (BHOB) should be determined as well.

Why is parallel measurement of insulin and C-peptide necessary?

If C-peptide is elevated along with insulin, it proves the endogenous origin of hyperinsulinism. If C-peptide is low, but insulin is high, exogenous insulin administration can be suspected (see ► Chap. 47).

◘ **Table 46.1** Results of the 72-hour fasting test in the patient and its trends according to the causes of hypoglycemia. *OAD* oral antidiabetic drug (sulfonylurea [SU] and glinides). *nd* non-determined. The patient produced the typical symptoms of hypoglycemia at 6 hours after beginning the test, and the test was then discontinued

	Patient's case	Insulinoma	Normal fast	Exogenous insulin	Use of OAD
Symptoms	*Yes*	Yes	No	Yes	Yes
Glucose	*28* mg/dL	<55 mg/dL	↓	↓↓	↓↓
Insulin	*7.0* μIU/mL	≥3 μIU/mL	↓	↑	↑
C-peptide	*2.2* ng/mL	≥0.6 ng/mL	↓	↓	↑
Proinsulin	*>134* pmol/L	≥5 pmol/L	↓	↓	↑
Ketones	*0.02* mmol/L	≤2.7 mmol/L	↑↑↑	↓	↓
Δ Glucose after glucagon	*nd*	≥25 mg/dL	< 25 mg/dl	≥ 25 mg/dl	≥ 25 mg/dl
Screening for SU, glinides	*nd*	Negative	Negative	Negative	Positive

What can be the relevance of proinsulin and β-hydroxy-butyrate measurement?

Proinsulin is a precursor of insulin and mostly decomposed in the insulin granule. Only 10% is released into the blood, which also lowers the blood sugar levels. Proinsulin continuously produced by a rare variant of proinsulinoma plays a role similar to the insulin produced by an insulinoma.

BHOB concentrations are lower in insulinoma patients because of the antiketogenic effect of insulin. A progressive rise in ketones after 18 hours of fast is indicative of a negative fast. BHOB values, as well as the glucose response to glucagon, can be helpful in patients in whom insulin and C-peptide values are in the borderline range.

How can we differentiate exogenous sulfonylurea or glinide administration from endogenous hyperinsulinism?

Sulfonylureas and the rarely given glinides are antidiabetic drugs acting via increasing endogenous insulin release from pancreatic beta cells (insulin secretagogue drugs). Therefore, both insulin and C-peptide are high in individuals taking sulfonylureas and glinides, and the fast test can be false positive. If there is suspicion for this, measurement of sulfonylureas or glinides is warranted.

Is chromogranin A (CgA) a sensitive marker for insulinoma?

CgA is a general marker for neuroendocrine tumors. For insulinoma, however, it is not particularly reliable.

What can be done for localizing the insulinoma?

Insulinomas are mostly solitary and small; therefore, their localization can be a great challenge. Classical transabdominal ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) should be regularly performed and in many cases can help to find the tumor. However, small tumors are often missed by these standard techniques. Endoscopic ultrasound (EUS) has high sensitivity to find small pancreatic tumors. In contrast with other neuroendocrine tumors, insulinoma usually expresses fewer receptors for somatostatin, and therefore, somatostatin-based functional imaging is less sensitive than in other neuroendocrine neoplasms; however, it can be tried.

Results of imaging in the Patient's case:

In our case localization diagnostics with abdominal ultrasound (no lesion), MRI pancreas (no lesion), ^{68}Gallium-DOTANOC positron emission tomography (PET)/ computed tomography (CT) (tracer uptake in cauda), DOPA PET/CT (no tracer uptake), and endoscopic ultrasound (four small tumors in the pancreas head and body) showed different results with suspected lesions in the head of the pancreas but also in the body and tail. Evaluation of diagnostic images was difficult due to signs of chronic pancreatitis. The results of the fine-needle aspiration biopsies of two masses during EUS were inconclusive and the patient suffered from postinterventional acute pancreatitis.

What can be done?

An interventional radiological technique, selective arterial calcium stimulation (SACT), can be performed to help the localization of insulinoma within the pancreas. The arteries supplying the pancreas (gastroduodenal, splenic, and superior mesenteric arteries) are cannulated and calcium is injected selectively. Calcium stimulates insulin release from hyperfunctional beta cells (i.e., insulinomas), and blood is taken from the hepatic veins to measure insulin. By this technique, the part of the pancreas can be identified where the insulinoma is harbored.

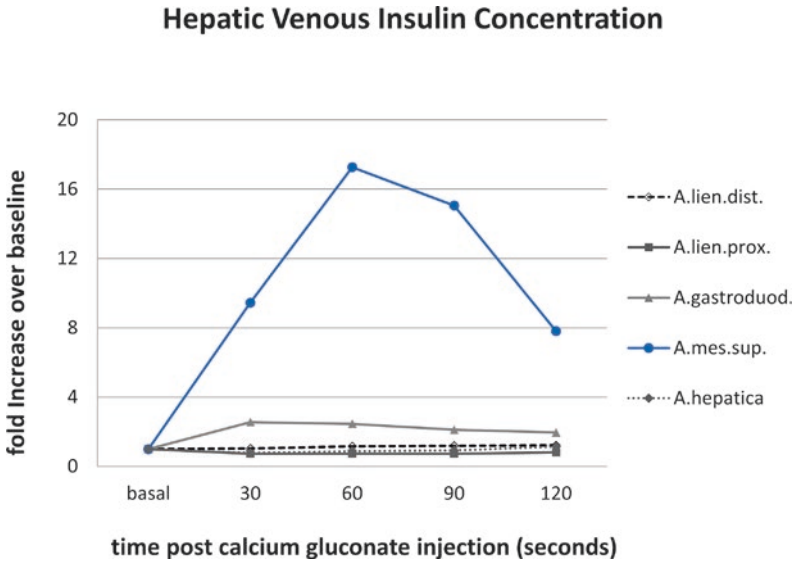

Fig. 46.1 Hepatic venous insulin concentrations at baseline and 30, 60, 90, and 120 seconds after arterial injection of calcium gluconate during SACT

SACT was performed in our case, and it showed a significant insulin release with a 17-fold increase from basal in the area of superior mesenteric artery as illustrated in Fig. 46.1.

What is nesidioblastosis?

Clinically termed as non-insulinoma pancreatogenous hypoglycemia syndrome, this pathological condition is characterized by hypertrophy of pancreatic beta cells. In contrast to insulinoma, it mostly leads to postprandial hypoglycemia, whereas insulinoma results in fasting hypoglycemia. Roux-en-Y gastric bypass surgery can lead to nesidioblastosis.

How should insulinoma be treated?

The treatment of insulinoma is primarily surgical, that is, enucleation of the tumor, or partial pancreatectomy. In patients non-eligible for surgery, and the tumor can be precisely localized, radiofrequency ablation can also be tried.

In the patient's case, after the SACT and a repeated EUS with localization of a hyperechogenic tumor in pancreas head, an enucleation of this tumor was performed. Intraoperative ultrasound and manual palpation did not reveal further masses. Intraoperative rapid section diagnostic and later histologic diagnostic did not show neuroendocrine tumor cells.

Are there drug options that reduce the severity and frequency of hypoglycemic episodes?

The drug diazoxide inhibits insulin secretion and therefore can help to alleviate hypoglycemic symptoms. Its major side effect includes edema. The Ca-antagonist verapamil can also be tried, but it is less effective. Whereas somatostatin analogues are very effective in controlling several neuroendocrine tumor-associated syndromes, e.g., carcinoid syndrome, glucagonoma, and VIP-oma, their efficacy in insulinoma is variable.

In malignant insulinoma, everolimus, an inhibitor of mechanistic target of rapamycin (mTOR) signaling, can be effective along with systemic chemotherapy (e.g., with streptozotocin).

Results of the post-surgical follow-up:

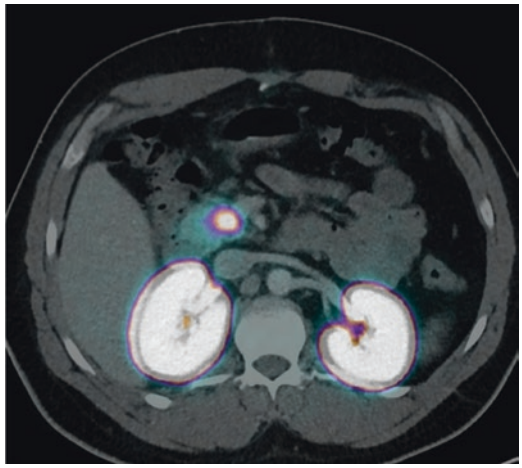

Fig. 46.2 A representative imaging picture of the ^{68}Ga-DOTA-Exendin-4 PET-CT showing the intensive isotope uptake of a small tumor in the lower part of the pancreas head ventral to the inferior vena cava

Postoperative severe hypoglycemia continued, which could only be controlled by combination therapy with somatostatin analogue (pasireotide) and diazoxide, and further diagnostic work-up was planned after the patient recovered from surgery.

How could we localize the insulinoma more precisely?

A novel nuclear imaging technique based on the expression of glucagon-like peptide 1 (GLP-1) receptor on beta cells is reported to have high sensitivity and specificity for detecting insulinoma. The imaging (^{68}Ga-DOTA-Exendin-4 PET-CT) was performed at the Nuclear Medicine Institute of the University of Basel (Switzerland). The 16 × 8 mm tumor has been localized to the lower part of the pancreas head next to the inferior vena cava and the superior mesenteric vein (Fig. 46.2).

Result of the repeated surgical intervention:

The second enucleation of this tumor was successful, and the patient was free of hypoglycemia after the removal of a histologically verified insulinoma.

Should we look for a hereditary tumor syndrome in patients with insulinoma?

The multiple endocrine neoplasia (MEN1) syndrome is associated with duodenopancreatic neuroendocrine tumors that are found in 30–80% of affected patients. Gastrinoma is most commonly associated with MEN1, but rarely, insulinoma might also occur. MEN1 testing should be proposed to young patients suffering from insulinoma and if there is suspicion of other manifestations (e.g., hypercalcemia suggestive of primary hyperparathyroidism) and certainly if there is positive family history.

Tips

- The reader is advised to read the following chapter on factitious hypoglycemia (▶ Chap. 47), and also multiple endocrine neoplasia type 1 (▶ Chap. 50).

Take Home Messages

- Insulinoma is a rare neuroendocrine tumor resulting in fasting hypoglycemia.
- The diagnosis is based on the fasting test with concomitant measurements of blood glucose, insulin, and C-peptide.
- Insulinoma is mostly a small solitary tumor, and therefore, its localization can be difficult warranting the use of several imaging modalities.
- Treatment is primarily surgical.

Suggested Reading

1. Christ E, Antwi K, Fani M, Wild D. Innovative imaging of insulinoma: the end of sampling? A review. Endocr Relat Cancer. 2020. https://doi.org/10.1530/erc-19-0476.
2. Hofland J, Kaltsas G, de Herder WW. Advances in the diagnosis and management of well-differentiated neuroendocrine neoplasms. Endocr Rev. 2019. https://doi.org/10.1210/endrev/bnz004.

3. Kann PH. Endoscopic ultrasound in endocrinology: imaging of the adrenals and the endocrine pancreas. Front Horm Res. 2016;45:46–54. https://doi.org/10.1159/000442277.
4. Marx SJ. Recent topics around multiple endocrine neoplasia type 1. J Clin Endocrinol Metab. 2018;103(4):1296–301. https://doi.org/10.1210/jc.2017-02340.
5. Masciocchi M. Pancreatic imaging. Endocrinol Metab Clin North Am. 2017;46(3):761–81. https://doi.org/10.1016/j.ecl.2017.04.006.
6. Murtha TD, Lupsa BC, Majumdar S, Jain D, Salem RR. A systematic review of proinsulin-secreting pancreatic neuroendocrine tumors. J Gastrointest Surg. 2017;21(8):1335–41. https://doi.org/10.1007/s11605-017-3428-8.
7. Oberg K. Management of functional neuroendocrine tumors of the pancreas. Gland Surg. 2018;7(1):20–7. https://doi.org/10.21037/gs.2017.10.08.
8. Qiao XW, Qiu L, Chen YJ, Meng CT, Sun Z, Bai CM, Zhao DC, Zhang TP, Zhao YP, Song YL, Wang YH, Chen J, Lu CM. Chromogranin A is a reliable serum diagnostic biomarker for pancreatic neuroendocrine tumors but not for insulinomas. BMC Endocr Disord. 2014;14:64. https://doi.org/10.1186/1472-6823-14-64.
9. Wang H, Ba Y, Xing Q, Cai RC. Diagnostic value of ASVS for insulinoma localization: a systematic review and meta-analysis. PLoS One. 2019;14(11):e0224928. https://doi.org/10.1371/journal.pone.0224928.

Factitious Hypoglycemia

Peter Igaz

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_47

Opening

The previous chapter discussed the neuroendocrine tumor insulinoma leading to endogenous hyperinsulinism, and thus to spontaneous hypoglycemia. A major differential diagnostic challenge related to insulinoma is represented by the administration of exogenous insulin or drugs provoking hypoglycemia. This chapter discusses factitious hypoglycemia, when the patient deliberately provokes hypoglycemic attacks mostly related to psychiatric disease.

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Definition of the Disease

Factitious hypoglycemia represents a condition when the patient deliberately provokes hypoglycemic attacks by self-injecting insulin or taking drugs lowering blood glucose levels. This condition is mostly related to psychiatric disease.

Case Presentation

A 39-year-old female patient was referred to our center following severe episodes of repeated hypoglycemia.

Her history included type 1 diabetes mellitus diagnosed at the age of 18. She had repeated episodes of hypoglycemia following the launching of insulin treatment. Gastrointestinal or autoimmune background was investigated without any positive result. Ten years after the diagnosis of diabetes mellitus, insulin treatment was omitted due to repeated hypoglycemic events. Insulinoma (or nesidioblastosis (*see previous chapter*)) was suspected based on elevated insulin levels (five times higher than the normal baseline on an empty stomach), and there wasn't any morphological sign suggestive of insulinoma by computed tomography (there was no available information on C-peptide measurement). At the age of 29, a pancreatoduodenectomy was performed. Histological examination of the removed pancreas showed no beta-cell hyperplasia or tumor. Three years after the operation, the hypoglycemic attacks recurred, and insulin treatment was stopped again. The hypoglycemic attacks recurred even more frequently than before, and these were not alleviated by diazoxide. The possibility of factitious hypoglycemia was first raised at the age of 38, when during a hypoglycemic episode (blood glucose: 2.2 mmol/L) a high insulin level (39.9 μIU/mL) and low C-peptide (0.33 ng/mL) level were measured.

In the year before her admission to our hospital, she had almost daily hypoglycemic attacks, and on one occasion she even needed artificial ventilation for some days in an intensive care unit.

What test should be used to investigate the origin of hypoglycemia?

A 72-hour fast test is the investigation of choice. Patients with insulinoma mostly produce spontaneous hypoglycemia within 48 hours after beginning the test and the laboratory-confirmed hypoglycemia is accompanied by elevated insulin and C-peptide (see previous ▶ Chap. 46 on insulinoma).

Here the patient presented significant hypoglycemia associated with neuroglycopenia one hour after admission to the hospital. Blood glucose level was 0.3 mmol/L,

and the insulin level taken at the same time was 27.35 μIU/mL, whereas C-peptide level was 0.01 ng/mL. The constellation of hypoglycemia associated with high insulin and very low C-peptide levels was repeatedly observed during her hospital stay.

Case Presentation Continued

Factitious hypoglycemia was thus confirmed that seemed to be provoked by exogenous insulin administration. The patient first denied the administration of insulin, but later the insulin-injecting device was found, and she admitted the use of insulin to induce hypoglycemia. Psychiatric treatment was proposed.

It can be hypothesized that the patient began to provoke hypoglycemic attacks shortly after the diagnosis of diabetes mellitus type 1 and even agreed to a pancreatoduodenectomy to mask the true origin of the repeated hypoglycemic attacks. Unfortunately, the documentation preceding the operation was only partially available, and there were no data on C-peptide measurements. Since the histology of the removed pancreas did not find any tumor or beta-cell hyperplasia, we can hypothesize that factitious hypoglycemia was responsible for the repeated hypoglycemic attacks during her whole disease history. Another, less probable explanation might be that she had an insulinoma but continued to provoke hypoglycemic attacks after the operation deliberately with insulin self-injection. Diazoxide that is an inhibitor of insulin release was certainly ineffective in preventing hypoglycemia provoked by the administration of exogenous insulin.

What kind of differential diagnostic problems might arise during the investigation for factitious hypoglycemia?

- Commercially available insulin measuring kits have varying sensitivity for detecting insulin analogues. It may therefore occur that both the measured insulin and C-peptide concentrations are low in a patient using novel insulin analogues.
- Anti-insulin autoantibodies might interfere with insulin measurements. Anti-insulin antibodies were previously considered to be a reliable sign of factitious hypoglycemia elicited by exogenous insulin injection, as these antibodies were thought to be absent from individuals having not encountered with exogenous insulin before. Later, however, it was found that anti-insulin antibodies might occur due to autoimmune disease, and therefore their presence cannot be considered as a reliable marker for factitious hypoglycemia.
- If the patient takes insulin secretagogue drugs (sulfonylureas and glinides) that stimulate endogenous insulin release, both insulin and C-peptide levels will be elevated. This is the most difficult clinical scenario, and the measurement of sulfonylureas (or the rarely used glinides) is a mainstay of diagnosis.
- Low insulin and C-peptide levels associated with hypoglycemia might also be rarely caused by paraneoplastic hypoglycemia (nonislet cell tumor hypoglycemia) that is mostly related to the production of insulin-like growth factor 2 (IGF-2) by the tumor (e.g., mesenchymal tumors and mesothelioma).

Tips

The reader is advised to read the previous chapter on insulinoma (▶ Chap. 46). Another major differential diagnostic problem related to an endocrine disease that is also linked to psychiatric disease is represented by primary polydipsia, discussed in ▶ Chap. 9 on diabetes insipidus.

Take Home Messages

- Factitious hypoglycemia is a deliberately induced condition either by injecting insulin or by taking glucose-lowering drugs.
- The diagnosis is based on the fasting test with concomitant measurements of blood glucose, insulin, and C-peptide levels.
- In contrast to insulinoma, if the patient injects exogenous insulin to provoke hypoglycemia, insulin level will be high and C-peptide level will be low. Analogous insulins, however, are not always measured by conventional insulin measuring kits that can cause further difficulties.
- It is most difficult to differentiate insulinoma from factitious hypoglycemia caused by insulin secretagogue drugs (sulfonylureas or glinides), as these induce endogenous insulin + C-peptide release.

Suggested Reading

1. Bauman V, Sturkey AC, Sherafat-Kazemzadeh R, McEwan J, Jones PM, Keating A, Isganaitis E, Ricker A, Rother KI. Factitious hypoglycemia in children and adolescents with diabetes. Pediatr Diabetes. 2018;19(4):823–31. https://doi.org/10.1111/pedi.12650.
2. Grunberger G, Weiner JL, Silverman R, Taylor S, Gorden P. Factitious hypoglycemia due to surreptitious administration of insulin. Diagnosis, treatment, and long-term follow-up. Ann Intern Med. 1988;108(2):252–7. https://doi.org/10.7326/0003-4819-108-2-252.
3. Neal JM, Han W. Insulin immunoassays in the detection of insulin analogues in factitious hypoglycemia. Endocr Pract. 2008;14(8):1006–10. https://doi.org/10.4158/ep.14.8.1006.
4. Wazaify M, Abushams L, Van Hout MC. Abuse of sulfonylureas: is factitious hypoglycemia a cause for concern? Int J Clin Pharm. 2019;41(1):3–5. https://doi.org/10.1007/s11096-018-0767-9.

Gastrinoma

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Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_48

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Opening

Gastrinoma is a rare gastrin-producing neuroendocrine tumor usually associated with a clinical picture of dyspepsia, diarrhea, and peptic ulcer disease first described by Zollinger and Ellison in 1955.

More than 60 years after its revelation, Zollinger-Ellison syndrome remains a challenging condition, and a high degree of suspicion is warranted to establish the diagnosis and perform necessary confirmatory testing. The mainstays of management comprise gastric acid output control, curative surgery, and systemic anti-tumoral therapies in advanced disease.

Definition of the Disease

The Zollinger-Ellison syndrome (ZES) is caused by a gastrin-secreting neuroendocrine tumor (neoplasm), also referred to as gastrinoma. The annual incidence is 0.1–3 cases per million, with a slight female preponderance. The majority of primary tumors originate in the duodenum and less frequently in the pancreas, stomach, lymph node, liver, and ovary. The main disease variant has a sporadic occurrence, and about 25% of gastrinomas are associated with the hereditary syndrome Multiple Endocrine Neoplasia type 1 (MEN1).

The key factor in the pathophysiology of ZES is a trophic action of autonomously secreted gastrin on both parietal and enterochromaffin-like (ECL) cells. High gastrin levels prompt increased hydrochloric acid output through direct stimulation of parietal cells and histamine release from ECL cells. Chronic hypersecretion of gastric acid, if left untreated, almost invariably results in multiple, refractory peptic ulcers that could be found in an unusual location of distal duodenum or proximal jejunum. Other common symptoms of ZES comprise abdominal pain (75%), diarrhea (73%), heartburn (44%), and weight loss (17%). Occasionally, gastrinomas could be diagnosed incidentally in an asymptomatic patient.

Due to the disease rarity and complexity, patients with gastrinoma should be managed in specialized centers by a multidisciplinary team of experts. The current clinical case discussion aims to highlight the deciding aspects of managing patients with gastrinoma.

Case Presentation

A 51-year-old woman had presented at the family practitioner clinic with a six-month history of diarrhea and an unintentional weight loss of 5 kg. The patient's medical and family histories were unremarkable. The frequency of bowel movements was 4–5 times a day, and stool varied between liquid and semi-formed consistency, with no blood or mucus. There was no exposure to antibiotics or laxatives. The diarrhea was not ameliorated by fasting or diet changes, such as avoidance of lactose or gluten. Initial laboratory tests of complete blood count, renal function, electrolytes, and thyroid-stimulating hormone (TSH) levels were within the normal range. Infectious etiology was ruled out by stool culture and specimen analyses. Additionally, over the preceding month, the patient experienced intermittent episodes of heartburn and epigastric pain. As an initial management strategy, omeprazole was prescribed at a daily dose of 20 mg. Following a two-week medication course, diarrhea and heartburn symptoms were improved. When the patient stopped taking omeprazole, this resulted in the renewal of symptoms.

What clinical clues point to ZES diagnosis, and what could be other likely causes of the patient's symptoms?

Clinical manifestations of ZES significantly overlap with other more prevalent gastrointestinal disorders, thus requiring a high degree of suspicion to establish the diagnosis. Moreover, due to the widespread use of anti-acid agents, ZES symptoms may be masked at the early stages. Therefore, the diagnosis is often delayed by a mean of 5 years.

The patient's heartburn could reflect gastroesophageal reflux disease (GERD), and intermittent epigastric pain could be a symptom of autoimmune atrophic gastritis, Helicobacter pylori-associated gastritis, or peptic ulcer disease. However, none of these conditions, as a separate entity, would explain chronic diarrhea.

The broad differential diagnosis of chronic diarrhea includes infections and inflammatory or functional disorders. Symptom patterns and settings should be used to assess the likelihood of specific causes. The lack of improvement of the patient's diarrhea with fasting could point to a secretory mechanism. Moreover, the amelioration of diarrhea during treatment with omeprazole should raise the suspicion of ZES. In patients with gastrinoma, diarrhea precipitated by gastric acid hypersecretion is characterized by secretory and osmotic components. High acid output causes direct injury to the small intestinal mucosa, inactivation of pancreatic lipase, and precipitation of bile acids secondary to the low pH.

Case Presentation Continued

The patient's evaluation with abdominal ultrasonography (US) reported on three liver lesions with features suggestive of metastases. Histopathological assessment of the liver lesion obtained by US-guided transcutaneous biopsy reported a diagnosis of a well-differentiated neuroendocrine tumor (NET).

Which hormone hypersecretion syndromes may cause this clinical picture?

The co-occurrence of liver metastases of NET origin and chronic diarrhea raises the suspicion for a hormone-secreting tumor. Entities to be considered include serotonin-secreting carcinoid tumor (carcinoid syndrome), vasoactive intestinal peptide–secreting pancreatic tumor (VIPoma), advanced medullary thyroid carcinoma, or gastrinoma. Carcinoid syndrome most commonly manifests as flushing and increased bowel movements associated with liver metastases of small intestinal or lung neuroendocrine tumors that secrete serotonin directly into the systemic circulation, thus bypassing hepatic inactivation. A VIP hypersecreting tumor is characterized by high-volume secretory diarrhea with marked electrolyte abnormalities and acidosis from bicarbonate wasting. Significant hypercalcitoninemia in patients with advanced medullary thyroid carcinoma has been reported as a cause of profound secretory diarrhea. Finally, a diagnosis of gastrinoma should be considered in this particular case, as discussed further below.

Case Presentation Continued

The patient's hormonal panel evaluation revealed normal levels of serum vasoactive intestinal peptide, calcitonin, and 5-hydroxyindoleacetic acid (serotonin metabolite) in a 24-hour urine collection sample. Fasting serum gastrin level was 1345 pg/mL (upper normal value, <110) and the chromogranin A level was 412 ng/mL (upper normal value, <98).

What could be noticed from these hormonal panel results?

Fasting serum gastrin (FSG) is an initial biochemical test to be performed when gastrinoma is suspected. The gastrin levels in ZES are typically ten-fold the upper

level of normal (ULN). However, ZES-associated FSG values vary significantly and could overlap with levels seen in benign etiologies. Thus, hypergastrinemia is an essential but insufficient finding for the confirmation of ZES diagnosis.

Several non-neoplastic conditions may cause achlorhydria and a compensatory rise in the gastrin levels. Common causes of secondary hypergastrinemia include chronic autoimmune atrophic gastritis, *Helicobacter pylori* infection, and proton pump inhibitors (▶ Box 48.1). (Proton pump inhibitors and histamine H2 receptor blockers should be therefore discontinued before FSG measurement like chromogranin A (▶ Chap. 44).) Nevertheless, in the discussed case, the diagnosis of ZES is highly suggestive, given the presenting symptoms, elevated FSG levels, and evidence of metastatic NET to the liver.

Box 48.1 Differential Diagnosis of Hypergastrinemia

Causes

1. Hypergastrinemia (with hyperchlorhydria)

Gastrinoma
Antral G-cell hyperplasia
Isolated retained antrum
Gastric outlet obstruction
Hypercalcemia

2. Hypergastrinemia (with achlorhydria)

Autoimmune atrophic gastritis
Chronic proton pump inhibitors/H2 receptors blockers use
H. pylori infection
Post-vagotomy status

3. Altered gastrin metabolism

Chronic renal failure
Short bowel syndrome

Which further tests would confirm the diagnosis of ZES?

An endoscopic gastroduodenoscopy should be performed to assess mucosal injury in patients with long-standing high acid output and enable gastric fluids aspiration for pH measurement. The endoscopic examination may reveal prominent gastric mucosal folds, erosive inflammation, strictures, perforation, and ulcers, at unusual locations. However, 15% of patients with gastrinoma have no evidence of peptic disease, and diarrhea may be the sole presenting symptom.

In the setting of ZES, the hydrochloric acid secretion rate is 5–7 times higher than the physiologic rate. A gastric pH of <2 confirms the diagnosis of ZES. In equivocal cases (e.g., if gastrin is <10 ULN), a secretin stimulation test may be helpful as it results in a significant rise of serum gastrin levels in ZES patients (different criteria are used e.g., a rise of more than 50% or >120 or 200 pg/mL).

Case Presentation Continued

The patient's gastroduodenoscopy study revealed gastritis with no ulceration. The aspirated gastric fluid with pH <2 supported the diagnosis of gastrinoma.

What therapy should be initiated upon the diagnosis of ZES?

The mainstay of acid-reducing therapy consists of high-dose proton pump inhibitors (PPIs). These agents are well tolerated and have few long-term adverse side effects even with chronic use at high doses. PPIs inhibit both basal and stimulated gastric acid secretion, through binding to H^+/K^+-ATPase at the luminal aspect of the gastric parietal cells. Careful follow-up and instructions must be given to gastrinoma patients not to withhold PPIs therapy without prior consultation. Cases of perforations and recurrence of profound diarrhea leading to severe dehydration were reported when PPI-therapy had been interrupted.

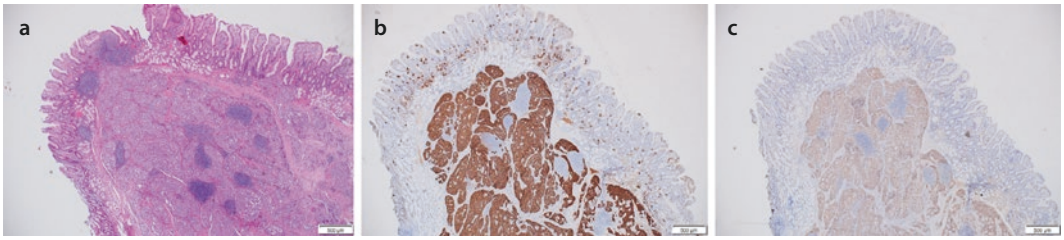

Fig. 48.1 Histopathological examination of the resected submucosal gastrinoma specimen. **a** Hematoxylin–Eosin (HE); **b** Chromogranin A positive immunohistochemical staining; and **c** Gastrin positive immunohistochemical staining

In the case presented, therapy with proton pump inhibitor esomeprazole at a dose of 40 mg twice a day was initiated, with a significant improvement in the patient's abdominal pain and diarrhea symptoms.

Which techniques are employed in the localization of primary lesions and staging of gastrinomas?

The localization of gastrinomas can be somewhat difficult, as tumors can be small and escape detection by conventional imaging modalities. Two-thirds of gastrinomas arise in the area called the "gastrinoma triangle" bordered by the second and third portions of the duodenum, the proximal body of the pancreas, and the confluence of the cystic and common bile ducts.

Since gastrinomas are vascular tumors, they may appear as enhancing lesions on contrast-enhanced computed tomography (CECT) and magnetic resonance imaging (MRI). Although CECT and MRI modalities have high specificity, the sensitivity is substantially decreased for <2 cm tumors. Concerning functional imaging, the positron emission tomography (PET) techniques significantly improved the localization of gastrinomas. Expression of somatostatin receptors on gastrinoma cells allows utilization of the radioisotope ^{68}Gallium ligated to a somatostatin analog. Somatostatin Receptor Imaging (SRI) (e.g., ^{68}Ga-DOTATATE PET-CT) for tumor detection has a higher sensitivity and specificity compared to CECT or MRI.

Additionally, endoscopic ultrasonography (EUS) has become an indispensable tool for the localization of small tumors that originate from the duodenal wall or the pancreas. During EUS evaluation, most intrapancreatic gastrinomas appear as hypoechoic, homogenous and solid lesions. Importantly, EUS-guided fine-needle aspiration allows tumor histopathological evaluation. Microscopic examination of gastrinoma typically reveals neuroendocrine tumor cells arranged in a nested and trabecular pattern, uniform nuclei with "salt and pepper" type chromatin. The immunostaining for chromogranin, synaptophysin, gastrin, and Ki67 is required for diagnosis and grading of the tumor (Fig. 48.1).

In some instances, all imaging modalities fail to locate gastrinoma, and exploratory surgery by an experienced surgeon is required to identify the tumor.

Case Presentation Continued

The patient underwent a ^{68}Ga-DOTATATE-PET-CT, which revealed an increased radiotracer uptake by a 1.2 cm lymph node adjacent to the second part of the duodenum and by three focal liver lesions suggestive of metastatic disease (Fig. 48.2).

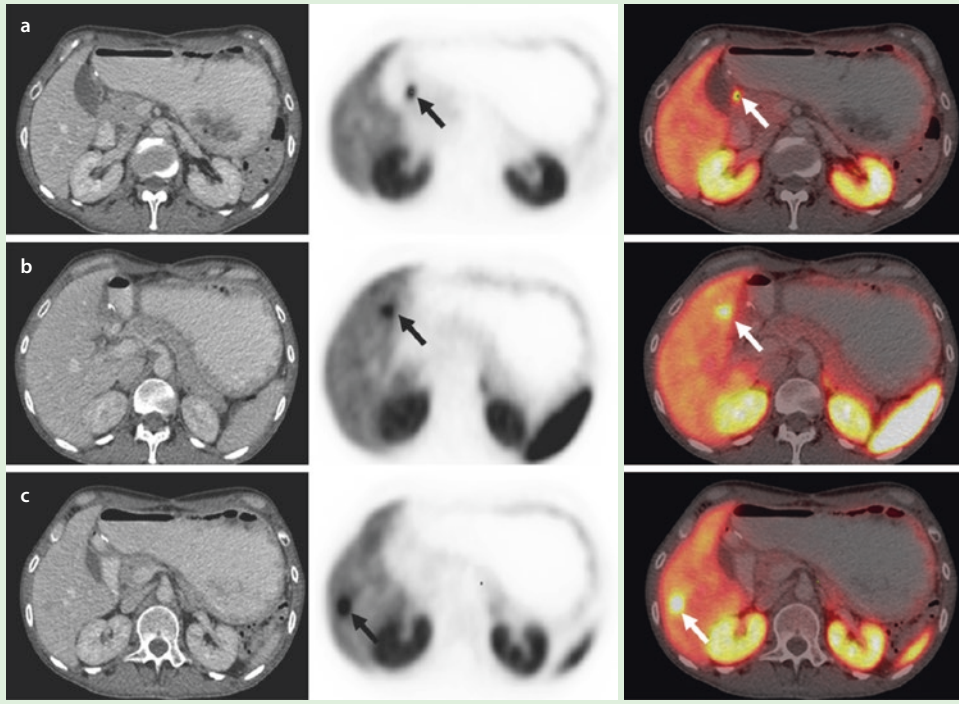

Fig. 48.2 ^{68}Gallium DOTATATE PET-CT axial images. **a** (top row) increased radiotracer uptake (arrow) in the peri-duodenal lymph node; **b** and **c** increased radiotracer uptake (arrow) in the metastatic liver lesions

Which other endocrinopathies should be considered in a patient with gastrinoma?

A number of gastrinomas is associated with Multiple Endocrine Neoplasia type 1 (MEN1), a hereditary cancer syndrome characterized by the predisposition to developing endocrine neoplasms, predominantly of parathyroid, gastroenteropancreatic, and pituitary origin (presented in detail in ▶ Chap. 51). Gastrinoma is the most common functional gastroenteropancreatic tumor in MEN1. In the setting of a hereditary syndrome, gastrinomas are diagnosed on average 10–20 years earlier than sporadic tumors, being commonly multiple, small, and primarily located in the submucosa of the duodenum (>80%), and less frequently within the pancreas (Table 48.1). In contrast with the sporadic gastrinomas, in MEN1, gastric ECL cells proliferation under chronic gastrin stimulation may result in the development of NET polyps, referred to as type 2 gastric carcinoids. The synchronous manifestation of MEN1-associated primary hyperparathyroidism may exacerbate ZES symptoms and complicate its' management. Hypercalcemia stimulates gastrin secretion via calcium-sensing receptors expressed on the surface of gastrinoma cells and therefore it should be addressed first. In MEN1 patients, ZES could present as a first manifestation of the syndrome. Thus, the possibility of MEN1 diagnosis should be considered in all gastrinoma patients, mainly in young ones (< 40 years old) and in those with suggestive family history.

Table 48.1 Comparison of sporadic and MEN1-associated gastrinomas

Clinical characteristics	Sporadic gastrinoma	MEN1-associated gastrinoma
Prevalence	75%	25%
Family history	No	Yes
Onset	40–60 years	20–40 years
Tumor multifocality	Single primary lesion	Multiple primary lesions
Concurrent endocrinopathies	None	Prevalent
Concurrent gastric carcinoid polyps	No	Yes
Surgical cure rate	60%	Rare

In our case, the patient's age at presentation, exclusion of primary hyperparathyroidism by biochemical testing, and absence of family members with characteristic endocrine tumors made the MEN1 association unlikely.

Which considerations should be taken into account before the decision on a surgical procedure in gastrinoma patients?

Following the first step of acid-reducing therapy with PPIs, surgical resection is indicated for localized disease with the intention to cure. Notably, this approach differs for sporadic and MEN1-associated tumors, the latter being a subject of controversy, as MEN1 patients are exceptionally rarely cured by removing the suspected primary tumor. In sporadic gastrinomas, complete surgical resection also proves to be challenging at times. Although the postoperative cure rates approach 60%, the disease recurs within 5 years in about half of these patients. Nevertheless, in the operated patients, a 20-year disease-specific survival reaches 98%. For primary tumor resection, a Kocher maneuver must be performed to explore the structures lying within the gastrinoma triangle area. A thorough duodenal examination includes endoscopic transillumination and duodenotomy to facilitate the identification of small submucosal tumors by manual palpation. The tissue sparing surgery, such as enucleation, is preferable for small pancreatic tumors, while the larger tumors may require more extensive resection. Due to the 30–70% risk of lymph node metastases, even in small primary tumors, the dissection of regional lymph nodes is mandatory. The presence of metastatic liver disease significantly worsens prognosis and decreases survival. Surgical resection should be advocated for patients with oligometastatic liver disease if sufficient size and function of the remnant liver can be ensured. If a complete hepatic metastases resection is unachievable, the 70–90% debulking of tumor burden has been reported to improve disease-specific survival rates. Radiofrequency ablation (RFA), an adjunct parenchymal-sparing procedure for small bilobar liver metastases, may be utilized during the surgery, thus allowing better tumor control. Finally, prophylactic cholecystectomy should be performed to avoid gallstone complications from potential future somatostatin analogs (SSAs) therapy for recurrent disease.

What are the available systemic therapies in the management of metastatic gastrinoma?

The high expression of somatostatin receptors in gastrinomas makes SSA therapy a rational option in non-operable disease as both anti-secretory and anti-tumoral agents. The evidence of the anti-proliferative effect of SSA is well established based on data from randomized controlled studies, showing improved progression-free survival in treated NET patients. SSAs demonstrated a long-lasting anti-tumoral effect in up to 50% in small series of patients with metastatic gastrinomas. Furthermore, patients whose disease progress with SSA therapy may ben-

efit from the administration of Peptide Receptor Radionuclide Therapy (PRRT) that combines SSAs with a therapeutic dose of the radionuclides (e.g., Lutetium 177). Additionally, patients with the liver-predominant metastatic disease could benefit from liver-directed therapies that include transarterial (chemo-)embolization (TACE/TAE) or selective internal radiation therapy (SIRT). Targeted therapies with the mechanistic target of rapamycin (mTOR)-inhibitor everolimus, the tyrosine kinase inhibitor sunitinib, and chemotherapy (e.g., capecitabine-temozolomide (CAPTEM) regimen) could be considered in selected patients. However, more studies are warranted to elucidate the role of these therapies, specifically for gastrinoma patients.

What are the main prognostic factors in gastrinoma patients?

- The primary determinants of survival in gastrinoma patients are the initial FSG levels above ≥20 ULN, tumor size, liver metastases, a pancreatic origin, the tumor grade, and older age at diagnosis. Notably, survival does not appear to be affected independently by lymph node metastasis or MEN1 mutation.

- The major prognostic factor is the presence and the burden of liver metastasis. Patients with liver metastases at initial presentation have a worse 10-year survival rate than those who develop metastases later in the course of the disease. From an oncological perspective, surgery offers a significant survival advantage compared to non-operative management. Operated patients have a significantly less chance of developing liver metastases (5% vs. 29%), and better overall survival (81% vs. 55%) rates.

Case Presentation Concluded

Based on the preoperative investigations, the patient underwent surgical exploration that included duodenal mobilization and careful examination of the gastrinoma triangle area, with the visualization and resection of the suspicious nodule, which corresponded to the 1.2 cm lesion with increased radiotracer uptake seen on preoperative ^{68}Ga-DOTATATE positron emission tomography-computed tomography (PET-CT). Duodenotomy with manual wall palpation and intraoperative ultrasound assessment of the pancreas revealed no other lesions. Multiple bilobar hepatic lesions were identified and treated with the microwave ablation antenna.

The histopathological analysis of the resected nodule confirmed a 12 × 10 × 9 mm well-differentiated neuroendocrine tumor with positive staining for gastrin that had almost entirely replaced a lymph node. The tumor proliferation index (Ki67) was 2% (grade 1).

The operative and histopathological findings indicated the diagnosis of primary lymph node gastrinoma with liver metastases. One year after the surgery, the patient was asymptomatic and well. The postoperative evaluation suggested a surgical cure with normal FSG levels of 69 pg/ml (upper normal value, <110), and no evidence of disease on follow-up imaging.

Tips

The reader is advised to read the chapters on carcinoid syndrome (► Chap. 44) and Multiple Endocrine Neoplasia type 1 (MEN1, ► Chap. 51). Several aspects of neuroendocrine tumor treatment are discussed in ► Chap. 44 on carcinoid syndrome. The differential diagnosis of endocrine tumor-related chronic diarrhea is also discussed in the chapter on medullary thyroid cancer (► Chap. 19).

Take Home Messages

- Gastrinoma is a gastrin-producing neuroendocrine tumor resulting in a clinical picture of epigastric pain, diarrhea, and peptic ulcer disease known as Zollinger-Ellison Syndrome.
- Most gastrinomas occur sporadically, and 25% are associated with Multiple Endocrine Neoplasia type 1 (MEN1).
- Confirmatory testing includes elevated fasting serum gastrin levels (typically a ≥ ten-fold increase) and low gastric pH (<2).
- Somatostatin receptor imaging has higher tumor detection rates than CT or MRI. Endoscopic ultrasound is helpful for the detection of sub-centimeter, multi-focal, duodenal, and pancreatic gastrinomas.
- Initial treatment with high dose proton pump inhibitors is mandatory to reduce gastric acid production, and it should be continued chronically in patients with persistent disease.
- Surgery should be considered in patients with resectable disease. In advanced cases, systemic therapies are available for selected patients, such as somatostatin analogs (SSAs), Peptide Receptor Radionuclide Therapy (PRRT), liver-locoregional therapies, everolimus, sunitinib, and capecitabine-temozolomide (CAPTEM) regimen.

Suggested Reading

1. Epelboym I, Mazeh H. Zollinger–Ellison syndrome: classical considerations and current controversies. Oncologist. 2014;19:44–50. https://doi.org/10.1634/theoncologist.2013-0369.
2. Giusti F, Cianferotti L, Boaretto F, Cetani F, Cioppi F, Colao A, Davì MV, Faggiano A, Fanciulli G, Ferolla P, Ferone D. Multiple endocrine neoplasia syndrome type 1: institution, management, and data analysis of a nationwide multicenter patient database. Endocrine. 2017;58(2):349–59. https://doi.org/10.1007/s12020-017-1234-4.
3. Goebel SU, Peghini PL, Goldsmith PK, Spiegel AM, Gibril F, Raffeld M, Jensen RT, Serrano J. Expression of the calcium-sensing receptor in gastrinomas. J Clin Endocrinol Metab. 2000;85:4131–7. https://doi.org/10.1210/jcem.85.11.6963.
4. Grozinsky-Glasberg S, Barak D, Fraenkel M, Walter MA, Müeller-Brand J, Eckstein J, Applebaum L, Shimon I, Gross DJ. Peptide receptor radioligand therapy is an effective treatment for the long-term stabilization of malignant gastrinomas. Cancer. 2011;117(7):1377–85. https://doi.org/10.1002/cncr.25646.
5. Metz DC, Comer GM, Soffer E, Forsmark CE, Cryer B, Chey W, Pisegna JR. Three-year oral pantoprazole administration is effective for patients with Zollinger–Ellison syndrome and other hypersecretory conditions. Aliment Pharmacol Ther. 2006;23:437–44. https://doi.org/10.1111/j.1365-2036.2006.02762.x.
6. Naswa N, Sharma P, Soundararajan R, Karunanithi S, Nazar AH, Kumar R, Malhotra A, Bal C. Diagnostic performance of somatostatin receptor PET/CT using 68Ga-DOTANOC in gastrinoma patients with negative or equivocal CT findings. Abdom Imaging. 2013;38(3):552–60. https://doi.org/10.1007/s00261-012-9925-z.
7. Peghini PL, Annibale B, Azzoni C, Milione M, Corleto VD, Gibril F, Venzon DJ, Delle Fave G, Bordi C, Jensen RT. Effect of chronic hypergastrinemia on human enterochromaffin-like cells: insights from patients with sporadic gastrinomas. Gastroenterology. 2002;123:68–85. https://doi.org/10.1053/gast.2002.34231.
8. Roy PK, Venzon DJ, Feigenbaum KM, Koviack PD, Bashir S, Ojeaburu JV, Gibril F, Jensen RT. Gastric secretion in Zollinger-Ellison syndrome. Correlation with clinical expression, tumor extent and role in diagnosis—a prospective NIH study of 235 patients and a review of 984 cases in the literature. Medicine. 2001;80:189–222. https://doi.org/10.1097/00005792-200105000-00005.
9. van Beek DJ, Nell S, Pieterman CR, de Herder WW, van de Ven AC, Dekkers OM, van der Horst-Schrivers AN, Drent ML, Bisschop PH, Havekes B, Borel Rinkes IH. Prognostic factors and sur-

vival in MEN1 patients with gastrinomas: results from the DutchMEN study group (DMSG). J Surg Oncol. 2019;120(6):966–75. https://doi.org/10.1002/jso.25667.
10. Wilcox CM, Seay T, Arcury JT, Mohnen J, Hirschowitz BI. Zollinger–Ellison syndrome: presentation, response to therapy, and outcome. Dig Liver Dis. 2011;43:439–43. https://doi.org/10.1016/j.dld.2010.11.007.
11. Zollinger RM, Ellison EH. Primary peptic ulcerations of the jejunum associated with islet cell tumors of the pancreas. Ann Surg. 1955;142:705–22.

Humoral Hypercalcemia of Malignancy

Júlia Lohinszky and Andrea Uhlyarik

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_49

Opening

Hypercalcemia is a quite common metabolic complication in cancer patients. The severe form of hypercalcemia could be a life-threatening condition, requiring immediate medical intervention. In this chapter, the endocrine form of malignancy-related hypercalcemia, that is humoral hypercalcemia of malignancy, will be discussed – that is the most common form of malignancy-related hypercalcemias. The management of hypercalcemia is also presented in this chapter.

49

Definition of the Disease

The diagnosis of hypercalcemia is confirmed if the serum calcium level is above the upper limit of the normal reference value (normal total serum calcium: 2.2–2.6 mmol/L or 8.82–10.62 mg/dL). Hypercalcemia affects approximately 20–30% of all cancer patients during the course of the disease. A positive cancer history could help in the diagnosis of malignancy-associated hypercalcemia (MAH), but hypercalcemia could also be the first sign of the disease. Malignancy-associated hypercalcemia is divided into four groups (Table 49.1):

1. *Humoral hypercalcemia of malignancy (HHM)* that is caused by the secretion of mainly Parathyroid Hormone-Related Protein (PTHrP) by several different malignancies including renal cancer, ovarian cancer, breast cancer, or squamous cell carcinomas of the lung, head, and neck cancers, esophagus cancer, and so on. The onset of hypercalcemia is usually associated with an advanced stage of the underlying malignant disease. The prognosis is poor, as the life expectancy does not exceed 6 months in the majority of the cases, and approximately 50% of patients decease within 30 days after diagnosis.

   PTHrP has high homology with parathyroid hormone and shares the same receptor. In normal conditions, however, PTHrP is mainly a local, paracrine mediator that does not have a role in the regulation of normal calcium homeostasis. The uncontrolled secretion of PTHrP by a malignant tumor as a form of a paraneoplastic endocrine syndrome leads to hypercalcemia.
2. *Local osteolytic hypercalcemia (LOH)*, that is due to metastatic bone destruction, for example, in multiple myeloma or breast cancer.
3. *Excessive 1,25-dihydroxyvitamin D (calcitriol) secretion*, observed in some types of lymphomas.
4. *Ectopic parathyroid hormone (PTH) secretion*, that is very rare.

The chapter discusses HHM, which is the most common form accounting for approximately 80% of all MAH. PTHrP elevates the serum calcium level by increasing bone resorption and enhancing the renal resorption of calcium like parathyroid hormone.

Table 49.1 Forms of malignancy-related hypercalcemias

Type of hypercalcemia	Frequency (%)	Typical related malignancies
Humoral hypercalcemia of malignancy (HHM)	80	Squamous cell carcinomas (esophageal, lung, head and neck, cervix) Breast, renal, bladder, ovarian, prostate, and colorectal cancer Hematological malignancies
Local osteolytic hypercalcemia (LOH)	20	Breast cancer Multiple myeloma Lymphoma
Excessive 1,25-dihydroxyvitamin D secretion	<1	Lymphoma
Ectopic parathyroid hormone (PTH) secretion	<1	Variable

Case Report

The 57-year-old female patient was diagnosed with a malignant tumor in her left breast. Preoperative staging (abdominal ultrasound, chest X-ray, bone scan) did not reveal distant metastases. The patient was operated: lumpectomy and sentinel lymph node biopsy were performed. The pathological diagnosis was an invasive ductal adenocarcinoma, pT2 (40 mm), ER (estrogen receptor): negative, PR (progesteron receptor): negative, HER2: +++, Ki-67: ~15%. Based on the pathological results, adjuvant chemotherapy and trastuzumab were indicated. Two cycles of epirubicin + cyclophosphamide combination were given. Before the third cycle, the patient was hospitalized because of weakness, constipation, nausea, and abdominal pain. Clinical findings at hospitalization: blood pressure 150/80 mmHg, HR 84/min, normal temperature, and mild dizziness.

What are the signs and symptoms of hypercalcemia?

Two main factors have significant role in the development of a symptomatic hypercalcemia: the level of serum calcium and the rapidity of its development. Hypercalcemia is severe if total serum Ca is >3.5 mmol/L (>14 mg/dL), whereas it is life-threatening over 4 mmol/L (>16 mg/dL). The suspicion of hypercalcemia should be based on clinical symptoms. Patients often complain about fatigue and anorexia. Clinical symptoms regularly affect four organ systems.

1. The neurological symptoms include muscle weakness, behavioral changes, disorientation, somnolence or coma, and posterior reversible leukoencephalopathy. A rapid increase of the serum calcium level frequently leads to severe neurologic dysfunction, while a chronic hypercalcemia could result in moderate symptoms.

2. The renal involvement could lead to acute kidney injury, nephrogenic diabetes insipidus, renal vasoconstriction, and distal renal tubular acidosis with consequential polyuria. The polyuria, along with the reduced fluid intake caused by the gastro-

Table 49.2 Clinical manifestation of hypercalcemia

Organ	Dysfunction
Cardiovascular	Arrhythmias, short QT interval, ST abnormalities, hypertension
Gastrointestinal	Nausea, vomiting, peptic ulcer disease, constipation, and acute pancreatitis
Neuropsychiatric	Behavioral changes, disorientation, somnolence or coma, posterior reversible leukoencephalopathy
Renal	Nephrolithiasis, acute kidney injury (nephrogenic diabetes insipidus with consequential polyuria), chronic renal insufficiency

intestinal symptoms, leads to severe fluid depletion that further aggravates hypercalcemia.

3. Gastrointestinal symptoms include nausea, vomiting, peptic ulcer disease, constipation, and in severe cases even acute pancreatitis.

4. Cardiovascular alterations include arrhythmias, short QT interval, ST abnormalities, and hypertension. The clinical symptoms are summarized in Table 49.2.

Case Report Continued

At the time of hospitalization, the patient's laboratory results were found as follows: serum calcium 4.9 mmol/L, serum BUN (blood urea nitrogen): 11.9 mmol/L (normal 2.8–7.2); creatinine: 177 μmol/L (normal: 59–104); Glomerular filtration rate (GFR): 26.9 ml/min/1.73 m2 (normal >90). Liver function was not altered, and no anemia, only a mild thrombocytopenia was observed. During the next 3 days, despite proper treatment her kidney function worsened, and hypercalcemia persisted. Abdominal ultrasound did not show any sign of metastatic intraabdominal spread. Thoracic radiography was also negative. Parathyroid hormone (PTH) level was low 8.7 pg/mL (normal range: 15.0–65.0) and 25-hydroxyvitamin-D was within the normal range. Serum albumin as well as the total serum protein levels were normal.

What kind of laboratory measurements should be performed?

Total serum calcium should be measured in any case of the clinical suspicion of hypercalcemia. Total serum calcium is a sum of two different forms. The free or ionized calcium is the physiologically active part (approx. 45–50%), while the other proportion is bound to carriers. The major carriers for calcium are proteins (approx. 40%) mostly albumin, while only a small proportion is bound to globulins. About 10–15% is bound to organic or inorganic anions. Any condition which influences the serum albumin level will also influence the total calcium levels. Hypoalbuminemia is frequent in cancer patients, therefore, it is strongly recommended to calculate the corrected total calcium level in these cases (see next question). There are several online formulas available. The measurement of free, ionized calcium level is another option.

The level of the PTH should also be routinely measured, since it is needed for the diagnosis of HHM, moreover, concomitant primary hyperparathyroidism is relatively frequently found in cancer patients and it is not associated with poor prognosis. 25-Hydroxyvitamin-D should be measured to exclude vitamin D-mediated hypercalcemia. The routine laboratory measurement, including renal function, blood count, and serum phosphorus level could help in treatment planning and monitoring.

How to correct serum calcium for alterations of serum albumin concentrations?

Any 10 g/L (1 g/dL) decrease in serum albumin concentration reduces the measured total calcium by 0.2 mmol/L (0.8 mg/dL). Therefore, 0.2 mmol/l (0.8 mg/dL) should be added to the measured total calcium for correction. For example, if the albumin levels are reduced by 20 g/L than the normal value, then 2 × 0.2 mmol/L (2 × 0.8 mg/dL) should be added to the measured serum calcium. (The other direction is also valid if hyperproteinemia is present.)

How can we differentiate between the various forms of hypercalcemias?

It should be kept in mind that despite the proven, advanced malignant disease, primary hyperparathyroidism must be excluded, as we discussed above. PTH measurement plays a key role in differential diagnosis. Elevated PTH level refers to primary hyperparathyroidism in most of the cases, but very rarely some tumors might also secrete PTH as an ectopic hormone. In case of normal or suppressed level of PTH (<20 pg/mL) and a proven diagnosis of an advanced solid tumor, the diagnosis of HHM can be established, and the measurement of PTHrP is not always required. The use of certain medications often given to cancer patients could also be related to hypercalcemia (thiazide diuretics, estrogens, tamoxifen, aminophylline, lithium, vitamins A-, and D); therefore revision of the concomitant medication is essential.

What kind of treatment options for hypercalcemia are available?

In case of severe, life-threatening hypercalcemia, the first step is volume expansion with intravenous saline infusion, at a rate of 200–300 mL/hour. After achieving proper rehydration (urinary excretion 100–150 mL/hour), calcitonin treatment is recommended at a dose of 4 IU/kg, intramuscularly or subcutaneously. The level of calcium should be carefully monitored, since not all patients are calcitonin sensitive. In case of detectable response, the calcitonin administration could be repeated every 6–12 hours. (Many years ago, calcitonin was widely used in the treatment of osteoporosis, but with the advent of more effective drugs, it is rarely used nowadays. In the treatment of acute hypercalcemia, calcitonin is effective as a rapidly acting drug.)

Intravenous bisphosphonates are very effective in reducing calcium levels, but they do not act very rapidly. Either zoledronic acid (4 mg) or pamidronate (60–90 mg) should be recommended. Zoledronic acid seems to be superior to pamidronate in reversing hypercalcemia. Ibandronate is also a therapeutic option. In case of severe renal impairment, bisphosphonates are contraindicated and therefore denosumab (a monoclonal antibody against RANKL (receptor activator of nuclear factor kappa-B ligand) inhibiting osteoclast activation) is another effective medical treatment.

Patients diagnosed with renal or heart failure should also be treated with loop diuretics (e.g., furosemide). Therapy refractory hypercalcemia accompanied with severe renal failure could be an indication for hemodialysis. Recovery is expected in 2–4 days after the initiation of therapy, but recurrence is very likely. Since the recurrence of hypercalcemia correlates with the progression of underlying disease, the initiation of proper anticancer treatment is also important. Patients with mild or asymptomatic hypercalcemia do not require immediate medical therapy.

Case Report Follow-Up

After 4 days of treatment, our patient started to recover and was discharged from the hospital after a week. As a summary of her history, primary hyperparathyroidism was excluded, since the level of PTH was below the normal. HMM was the most likely reason of the hypercalcemia, therefore, more precise restaging was recommended, since at the onset of the hypercalcemia there was no sign of an advanced disease. PTHrP levels can be measured for confirming the diagnosis.

What kind of imaging should be performed?

At the onset of a clinically significant hypercalcemia, the underlying malignant disease is usually already confirmed in the majority of cases. CT and/or magnetic resonance imaging (MRI) scans are considered as part of the regular staging procedures in cancer patients. Bone scan and ^{18}fluorodeoxyglucose-positron emission tomography-computed tomography (^{18}FDG-PET-CT) are both useful in detecting potential osseal metastases. Bone metastases should be excluded for confirming the diagnosis of MAH.

Case Report Continued

After recovering from hypercalcemia and having been discharged from the hospital, an ^{18}FDG-PET-CT was performed. It showed an advanced disease, as multiple small liver and lung metastases were seen. There was still no sign of bone metastases. Proper first line anticancer therapy was initiated, per protocol with a taxane and trastuzumab combination, but after 4 months, disease progression was observed. We lost our patient in 6 months.

Tips

The reader is advised to read the chapter on primary hyperparathyroidism (▶ Chap. 22) and also the chapter on osteoporosis (▶ Chap. 24) as drugs used in the treatment of hypercalcemia overlap with antiporotic medications.

Take Home Messages

- Severe hypercalcemia is a life-threatening complication.
- Humoral hypercalcemia of malignancy (HHM) is the most frequent form of malignancy-related hypercalcemias.
- In the absence of osseal metastases, the diagnosis of HMM is usually established if the level of PTH is normal or suppressed (<20 pg/mL), and the diagnosis of advanced malignant disease is already proven. PTHrP can also be measured.
- Fluid replacement, calcitonin, and bisphosphonates are the most important treatment options.
- Recurrence of hypercalcemia is very likely, as it is associated with the progression of the underlying malignant disease.
- The prognosis of hypercalcemia is poor, 50% of the patients die in 30 days, and the life expectancy is no more than 6 months.

Suggested Reading

1. Major P, Lortholary A, Hon JE, Mills G, Menssen HD, Yunus F, Bell R, Body J, Quebe-Fehling E, Seamanet J. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. J Clin Oncol. 2001;19(2):558–67. https://doi.org/10.1200/JCO.2001.19.2.558.
2. Mirrakhimov AE. Hypercalcemia of malignancy: an update on pathogenesis and management. N Am

J Med Sci. 2015;7(11):483–93. https://doi.org/10.4103/1947-2714.170600.
3. Pecherstorfer M, Schilling T, Blind E, Zimmer-Roth I, Baumgartner G, Ziegler R, Raue F. Parathyroid hormone-related protein and life expectancy in hypercalcemic cancer patients. J Clin Endocrinol Metabol. 1994;78(5):1268–70. https://doi.org/10.1210/jcem.78.5.8175989.
4. Ralston SH, Gallacher SJ, Patel U, Campbell J, Boyle IT. Cancer-associated hypercalcemia: morbidity and mortality. Clinical experience in 126 treated patients. Ann Intern Med. 1990;112(7):499–504. https://doi.org/10.7326/0003-4819-112-7-49.
5. Southby J, Kissin MW, Danks JA, Hayman JA, Moseley JN, Henderson MA, Bennett RC, Martin TJ. Immunohistochemical localization of parathyroid hormone-related protein in human breast cancer. Cancer Res. 1990;50(23):7710–6. Published December 1990.
6. Stewart AF. Hypercalcemia associated with cancer. N Engl J Med. 2005;352(4):373–9. https://doi.org/10.1056/NEJMcp042806.
7. Takeda K, Kimura R, Nishigaki N, Sato S, Okamoto A, Watanabe K, Yasui S. Humoral hypercalcemia of malignancy with a parathyroid hormone-related peptide-secreting intrahepatic cholangiocarcinoma accompanied by a gastric cancer. Case Rep Endocrinol. 2017;2017:7012520. https://doi.org/10.1155/2017/7012520.

Multiple Endocrine Neoplasia Syndromes

The final part of the book includes three very interesting but rare hereditary monogenic diseases where multiple endocrine tumors can develop in the same individual. The prototypes of multiple endocrine neoplasia syndromes (MEN**1** and MEN**2**) are presented in ► Chaps. 50 and 51, respectively. Von Hippel-Lindau syndrome, which can include pancreatic neuroendocrine tumors and pheochromocytoma as endocrine manifestations, is discussed in ► Chap. 52.

Contents

Multiple Endocrine Neoplasia Type 1

Aleksandra Gilis-Januszewska, Malgorzata Trofimiuk-Müldner, Anna Skalniak, and Alicja Hubalewska-Dydejczyk

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_50

Opening

In this chapter, the reader will get acquainted with the clinical features, diagnosis, and treatment of multiple endocrine neoplasia type 1 (MEN1). The parathyroid, neuroendocrine, and pituitary tumors that are part of the syndrome are also discussed in detail in different chapters.

Definition of the Disease

Multiple endocrine neoplasia type 1 is a rare genetic disorder with an autosomal dominant inheritance. Its overall prevalence is estimated at 1:30,000. Inactivating variants in the *MEN1* gene underlie most cases of the syndrome. The *MEN1* gene is located on chromosome 11q13, and its product, the protein menin, is a tumor suppressor controlling transcription, cell apoptosis, and epigenetic changes. Most of the pathogenic genetic alterations of *MEN1* are observed in a familial setting; however, in rare cases, the syndrome may be caused by a de novo mutation or genetic mosaicism.

MEN1 syndrome is characterized by a high penetrance of up to 95%. (Penetrance is a genetic term describing the likelihood of a given clinical manifestation for a genetic alteration.) Typical clinical manifestations of the MEN1 syndrome include tumors of the parathyroid glands, pancreas, and pituitary. Patients harboring disease-causing *MEN1* variants may also present with cutaneous lesions such as angiofibromas, collagenomas, or café au lait macules. The diagnosis of MEN1 can be established in three different ways: (a) clinically, with a confirmation of two or more MEN1-associated tumors in the same patient or (b) one tumor typical for MEN1 combined with a positive family history of a first-degree relative with clinical manifestation of MEN1, and (c) solely by genetic confirmation of a pathogenic germline *MEN1* variant in a symptomatic or asymptomatic patient. Primary hyperparathyroidism is the manifestation with the highest penetrance, and it is observed as the first symptom in most cases. Due to the pathological and hormonal variety of MEN1 neoplasms and their combinations, clinical manifestations may differ significantly in every individual (Table 50.1).

Table 50.1 Clinical presentation of MEN1-associated tumors

Tumor type	Organ	Secreted hormone(s)	Penetrance in MEN1 syndrome		Clinical manifestation
Parathyroid adenoma	Parathyroid glands	Parathyroid hormone	90%		Hypercalcemia: polydipsia, polyuria, nephrolithiasis, osteoporosis, constipation, peptic ulcer disease, muscle weakness, depression
Pituitary adenomas	Anterior pituitary	Prolactin	30–40%	20%	Females: oligo-/amenorrhea, galactorrhea, infertility Males: loss of libido, erectile dysfunction, infertility
		Growth hormone		10%	Acromegaly: coarsened facial features, hands and feet enlargement, impaired glucose tolerance or diabetes, hypertension heart failure,
		ACTH		5%	Cushing's disease: truncal obesity, proximal muscle atrophy, purple striae uncontrolled hypertension and diabetes
		Non-functioning		5%	Tumor mass effect (i.e., visual field defects), hypopituitarism
Gastroenteropancreatic neuroendocrine neoplasms	Gastrointestinal tract, pancreas	Gastrin	Pancreatic NENs 30–70%	Gastrinoma—40%	Zollinger–Ellison's syndrome: multiple peptic ulcers, refractory to treatment, esophagitis diarrhea
		Insulin		Insulinoma—10%	Fasting hypoglycemia: Nervousness, tremor, heart palpitations, sweating, hunger, fatigue, sleepiness, coordination and sight disturbances, seizures, coma
		Glucagon		Glucagonoma <1%	Migratory necrolytic erythema, diabetes, oral mucositis
		VIP		VIPoma <1%	Verner–Morrison's syndrome: secretory large-volume diarrhea, persisting during fasting, hypo-/achlorhydria, hypokalemia
		PP		Non-functioning and PP 20–55%	Abdominal pain, palpable tumor in the abdomen, weight loss

(continued)

Table 50.1 (continued)

Tumor type	Organ	Secreted hormone(s)	Penetrance in MEN1 syndrome		Clinical manifestation
Neuroendocrine tumors (carcinoid)	Lungs, bronchi, thymus, gastrointestinal tract	Serotonin, histamine, bradykinin, tachykinin	3%	BronchopulmonaryNEN 3%	Carcinoid syndrome when hormones escape the portal circulation:Cutaneous flushing erythematous pigmentation of facial and neck skin, diarrhea, fibrosis of tricuspid and pulmonary valves, heart failure, bronchospasm
				Thymic NET 2%	
				Gastro-entero-pancreatic NENs 10%	
Adrenal cortical adenoma	Adrenal gland	Cortisol	40%		Cushing's syndrome
Pheochromocytoma		Catecholamines	<1%		Elevated blood pressure (paroxysmal or resistant arterial hypertension), orthostatic hypotension, pallor, diaphoresis, anxiety, elevated heart rate, elevated blood glucose

MEN multiple endocrine neoplasia, *NEN* neuroendocrine neoplasm, *NET* neuroendocrine tumor, *PP* pancreatic polypeptide, *VIP* vasoactive intestinal peptide

Case Presentation

A 40-year-old woman was admitted to the Department of Endocrinology due to symptomatic hypoglycemia and suspicion of insulinoma. For the past 10 months, the patient had presented with sudden hunger with anxiety and irritability, tremor, and sweating. Symptoms disappeared after the consumption of carbohydrates. She gained 15 kg weight. During the routine laboratory examination (after an 8-hour fasting), her blood glucose level was 1.3 mmol/L and was accompanied by the above-mentioned symptoms. Abdominal ultrasonography scheduled by the GP revealed bilateral nephrolithiasis, but failed to show any pancreatic lesions.

The patient's medical history also included information on irregular menstrual cycles. She was pregnant twice at the ages of 25 and 28 and gave birth to two healthy daughters. For the last 5 years, she was unsuccessfully trying to conceive again—the consulting gynecologist diagnosed mild hyperprolactinemia, but after the administration of cabergoline (1 × 0.5 mg weekly), menstrual periods have become regular.

Since the age of 34, she has been suffering from nephrolithiasis. Mildly elevated serum calcium concentrations were found in the patient's medical records.

Family history: The patient's father died at the age of 48 due to apoplexy of previously unrecognized pituitary tumor. Her father and a 37-year-old sister were diagnosed with nephrolithiasis. Table 50.2 shows the patient's laboratory results on admission.

Table 50.2 Patient's laboratory results on admission

Parameter	Results on admission	Normal range
Glucose	2.89 mmol/L	3.30–5.60
Insulin	13.37 μU/mL	2.6–24.9
Serum calcium	2.73 mmol/L	2.15–2.55
Serum phosphate	0.6 mmol/L	0.81–1.45
Parathormone	232.5 pg/mL	14.90–56.90
Calcium urine excretion	12.51 mmol/24 h	2.5–8.0
Phosphate urine excretion	24.7 mmol/24 h	13.0–44.0
Prolactin	2478 μIU/mL	102–496
Luteinizing hormone (LH)	7.88 mIU/mL	2.4–12.6 in follicular phase
Follicle stimulating hormone (FSH)	2.26 mIU/mL	2.5–12.5 in follicular phase
Growth hormone (GH)	0.3 μIU/mL	0.2–10.0

What are the features and symptoms from this case which suggest MEN1 syndrome?

The patient's symptoms including hypoglycemia, nephrolithiasis with hypercalcemia, and hyperprolactinemia may suggest three concurrent neoplasms. Pancreatic insulinoma, primary hyperparathyroidism, and prolactin-secreting pituitary tumor develop typically in the course of MEN1 syndrome.

Primary hyperparathyroidism is the most prevalent manifestation of MEN1, observed in ≥90% of patients. Asymptomatic hypercalcemia is the most

frequent, but about 25% of patients have evidence of nephrolithiasis or nephrocalcinosis. In contrast to sporadic cases of hyperparathyroidism, diffuse parathyroid hyperplasia or multiple parathyroid adenomas are more common than solitary adenomas.

- Pancreatic neuroendocrine neoplasms (NENs) occur in 30–70% of patients with MEN1 syndrome. About 40% of pancreatic islet cell tumors originate from β-cells and secrete insulin, and they are diagnosed more frequently in patients younger than 40 years of age. About 60% of islet cell tumors originate from non-β-cell and often have a later onset (>40 years of age).

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- About 30% of pancreatic tumors are malignant and are disseminated at diagnosis. Malignant islet cell tumors occurring in MEN1 syndrome often have a less aggressive course than sporadic pancreatic NENs.

- Pituitary adenomas occur in up to 30–40% of patients with MEN1 syndrome, predominantly in the fourth decade of life, but various ages of onset have been noted (from 5 years to 90 years). The most prevalent subtype is prolactinoma (20%), followed by somatotropinoma (GH) (10%), corticotropinoma adrenocorticotropic hormone (ACTH) (5%), and non-functioning pituitary adenoma (NFPA) (5%). However, recent studies have shown increased frequency of NFPAs as a result of radiological screening of asymptomatic patients.

- Pituitary tumors in MEN1 patients appear to be larger and behave more aggressively than sporadic ones. Local tumor expansion may cause visual field defects, headaches, and hypopituitarism.

How can we diagnose insulinoma?

- Typical symptoms of hypoglycemia range from sudden hunger with anxiety and irritability, tremor and sweating, and may progress to confusion, slurred speech, loss of consciousness, seizures, coma, and death if physiological mechanisms fail to increase glucose concentration.

- The biochemical diagnosis of insulinoma is established in 95% of patients during a prolonged fasting (the classical fasting test lasts up to 72 hours). If at any time of the fasting test, plasma glucose decreases to a level of less than 55 mg/dL (or 3 mmol/L, previously 40 mg/dL—2.2 mmol/L), while concomitant serum insulin and C-peptide concentrations are elevated, the diagnosis is confirmed.

- Imaging could be challenging as many pancreatic lesions are very small and therefore not detectable by transabdominal ultrasound imaging, or even computed tomography (CT) and magnetic resonance imaging (MRI). In such cases, somatostatin receptor imaging, preferably positron emission tomography and computed tomography hybrid imaging (PET-CT) with ^{68}Ga-labeled somatostatin analogue (^{68}Ga-DOTATATE), can provide more conclusive information. As somatostatin receptor imaging may be less efficient in case of insulinomas, endoscopic ultrasonography may offer an alternative way of tumor detection. For insulinomas, radionuclide imaging with labeled glucagon-like peptide 1 (GLP-1) has also become recently available if other imaging modalities fail (▶ Chap. 46).

- Due to inconclusive results of the abdominal ultrasound, the patient underwent an MRI of the abdomen and pelvis, which revealed a pathological mass in the head of the pancreas (◘ Fig. 50.1). Subsequently, to determine the character of the pancreatic lesion, ^{68}Ga-DOTATATE PET-CT was performed. Excessive expression of somatostatin receptors in the pancreatic lesion suggested a neuroendocrine character of the tumor (◘ Fig. 50.2). (Insulinoma is discussed in detail in ▶ Chap. 46)

How can we diagnose primary hyperparathyroidism?

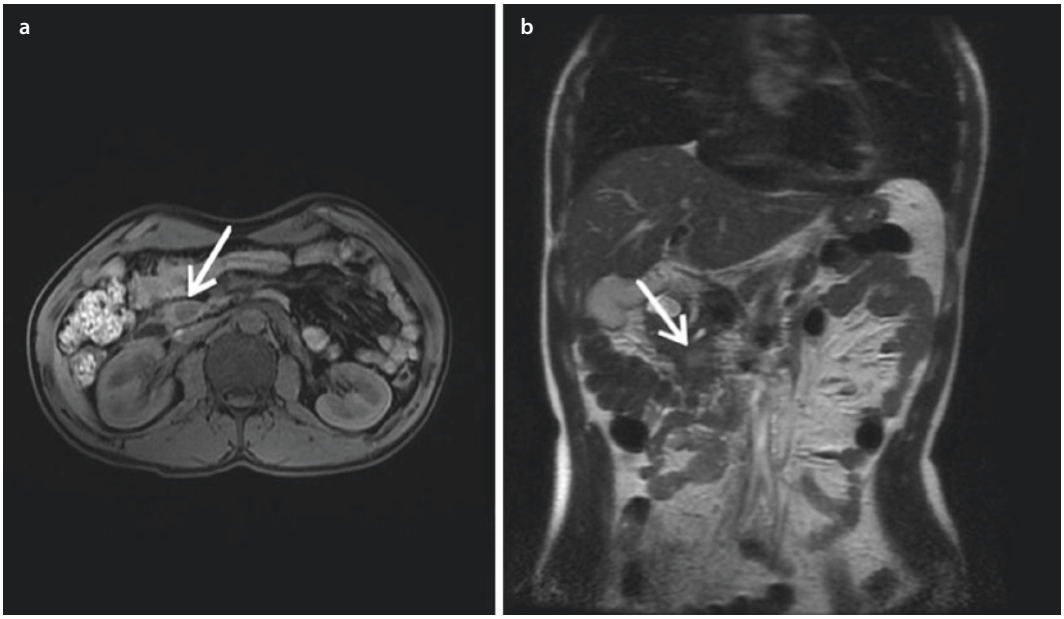

Fig. 50.1 Abdominal MRI: **a** axial T1 scan—a hypointense mass (arrow) nicely juxtaposed against the T1 hyperintense normal pancreatic parenchyma; **b** coronal T2 scan—the mildly hyperintensive mass (arrow) is visible in the head of the pancreas (Department of Diagnostic Imaging University Hospital in Krakow, Poland)

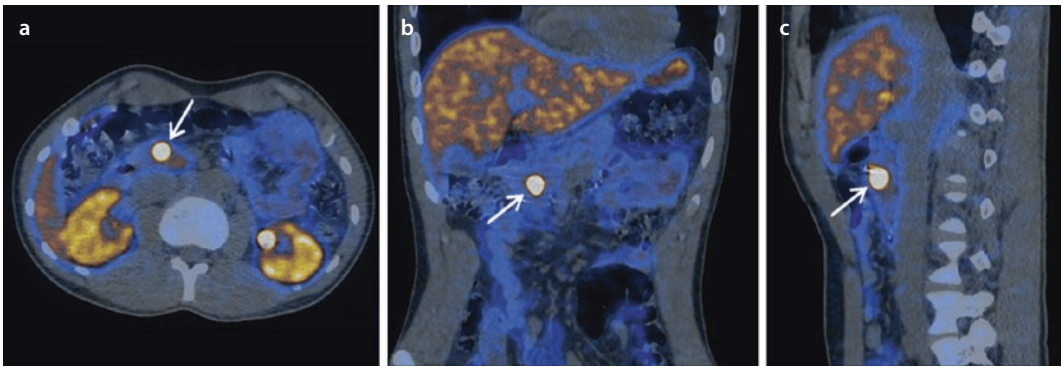

Fig. 50.2 Axial **a**, transverse **b**, and sagittal **c** fused [^{68}Ga]Ga-DOTATATE PET/CT images of a pancreatic (insulinoma) (arrows)

- Most patients with primary hyperparathyroidism have no symptoms at the time of diagnosis. However, typical symptoms of hypercalcemia include increased thirst, polyuria, and dehydration. Nephrolithiasis is the most common manifestation, but patients often complain about bone pain, weakness, depression, and confusion. Osteoporosis, especially with early onset, may be caused by hyperparathyroidism.
- Biochemically, elevated serum calcium level, decreased level of serum phosphate, increased level of parathyroid hormone, increased urinary calcium, and phosphate excretion are observed. Alkaline phosphatase concentration may be increased if bones are involved.
- Preoperative parathyroid imaging studies have great utility. The imaging techniques most frequently used are ^{99m}Tc-sestamibi

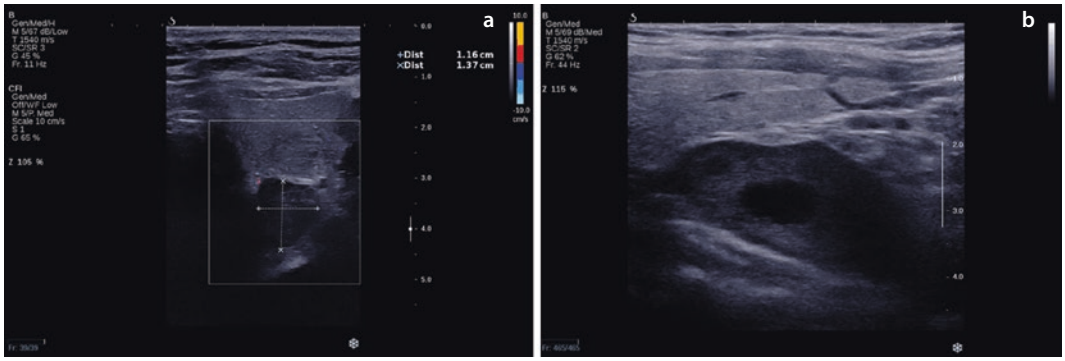

Fig. 50.3 Neck ultrasound (axial **a** and longitudinal **b** images)—a large well-defined hypoechoic mass posteroinferior to the left lobe of the thyroid gland is visible

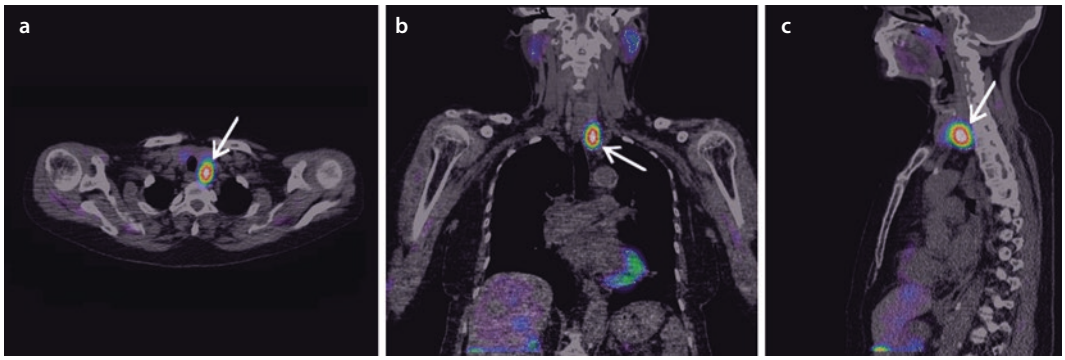

Fig. 50.4 A fused [^{99m}Tc]Tc-MIBI SPECT/CT of a left inferior parathyroid adenoma (*arrows*)—axial **a**, transverse **b**, and sagittal **c** images

scintigraphy, neck ultrasound, CT, and/or MRI. If scintigraphy and ultrasound results are concordant, the positive predictive value for correct localization of a parathyroid adenoma can be as high as 97%.

Neck ultrasound revealed a hypoechogenic mass located behind the posterior capsule of the thyroid (Fig. 50.3). ^{99m}Tc-sestamibi scintigraphy confirmed that it was an enlarged parathyroid gland (Fig. 50.4). (Primary hyperparathyroidism is discussed in detail in ▶ Chap. 22.)

How can we diagnose a prolactinoma?

Hyperprolactinemia usually manifests with abnormalities of menstrual cycles, galactorrhea, and infertility in females, and loss of libido and erectile dysfunction in male patients. The aforementioned symptoms constitute a reason for laboratory examination of prolactinoma.

Our patient also was referred to pituitary MRI, which detected a tumor in the anterior pituitary (most probably microadenoma) (Fig. 50.5). (Prolactinoma is discussed in detail in ▶ Chap. 1.)

Is it necessary to perform genetic screening to confirm MEN1 in a patient with clinical symptoms of the syndrome?

Although the clinical diagnosis of MEN1 syndrome does not require genetic testing for MEN1 mutations, it is advised in every case. Detailed diagnostic procedures recommended for patients with suspected MEN1 syndrome are summarized in Fig. 50.6.

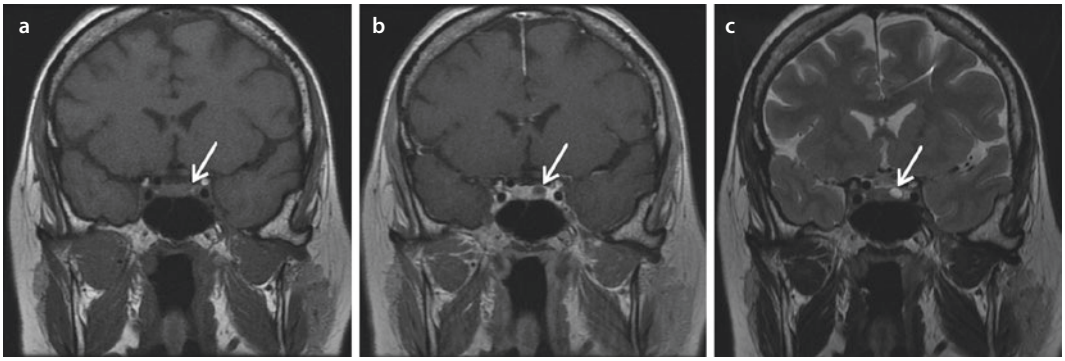

Fig. 50.5 Pituitary MRI. **a** Coronal T1 non-contrast image—a mass (arrow) isointense with the normal anterior pituitary; **b** coronal T1 contrast-enhanced image—a mass (arrow) in the left side of the sella, hypointense compared to intensely enhancing anterior pituitary; **c** coronal T2 image—a mass (arrow) in the left is hyperintense compared to the anterior pituitary (Department of Diagnostic Imaging University Hospital in Krakow, Poland)

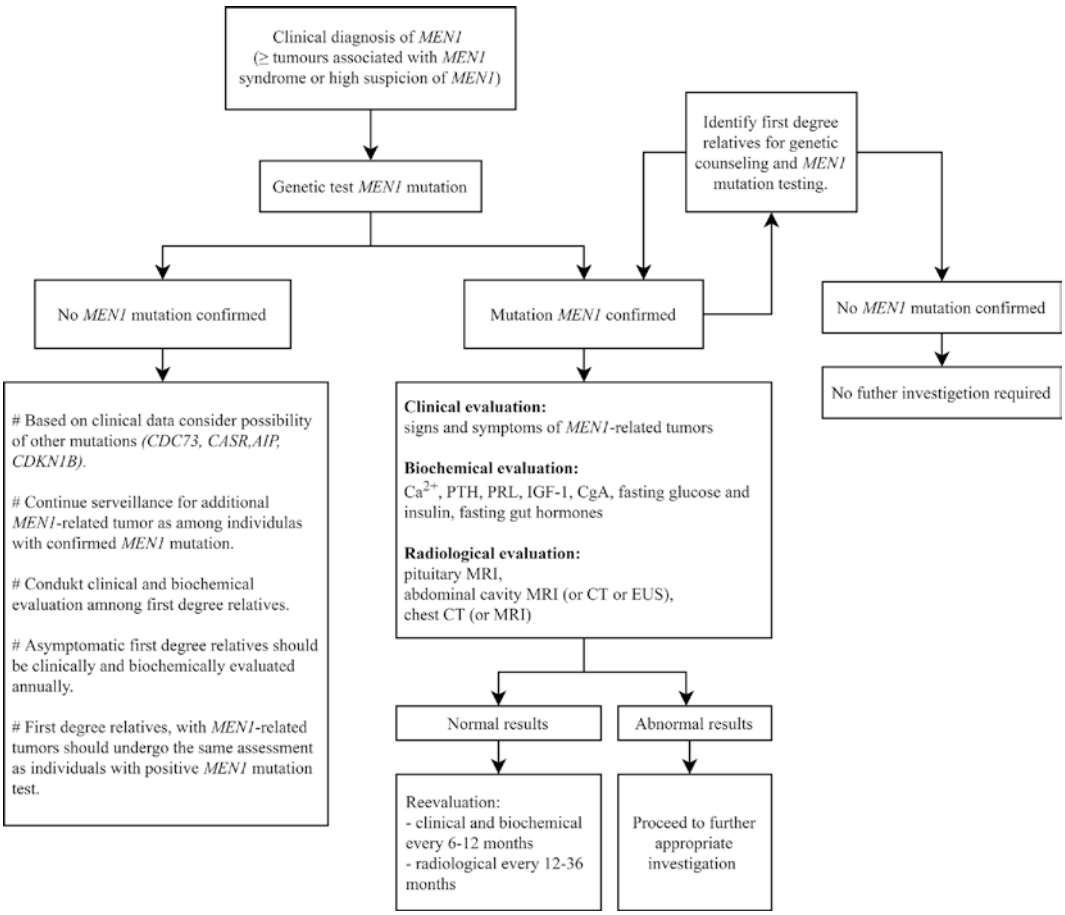

Fig. 50.6 Recommended diagnostic procedures and care for patients with suspected MEN1 syndrome. (Adapted from Thakker et al. 2012, *J Clin Endocrinol Metab*. Reprinted with permission of Oxford University Press.) Ca^{2+} ionized calcium, PTH parathyroid hormone, PRL prolactin, IGF-1 insulin-like growth factor 1, CgA chromogranin A, MRI magnetic resonance imaging, CT computed tomography, EUS endoscopic ultrasonography

What are the indications to perform genetic testing?

The diagnosis of MEN1 can be established in a patient without a first-degree relative having MEN1 if either one or both of the following criteria are fulfilled: (i) at least two of pituitary, parathyroid, and well-differentiated endocrine neoplasms of the gastro-entero-pancreatic tract and/or (ii) the presence of a (heterozygous) pathogenic variant of the *MEN1* gene. Because of the non-exclusive character of the above-mentioned criteria, it is reasonable to consider genetic testing in all patients who fulfill the above-mentioned criteria but also in unaffected patients whose family history is strongly indicative for MEN1 but for whom it is not possible to perform genetic testing in an affected family member, for example, because of them having passed away. After a pathogenic variant has been detected, genetic testing is also offered to first-degree family members of the mutation-carrier.

How is genetic testing being performed?

The reason for MEN1 development is an inheritable pathogenic variant in the gene *MEN1*. Since MEN1 is an autosomal dominant trait, only one allele needs to be mutated for a person to be predisposed, which means that patients with MEN1 will be heterozygotes (i.e., have one mutated copy of the *MEN1* gene and one copy with no pathogenic alteration). The detection of a pathogenic variant in a patient is an unequivocal evidence which allows to diagnose him/her with the MEN1 syndrome. Inherited genetic variants are present in all cells of the body, and therefore, no particular tissue source is needed to perform the diagnostic procedure. The material of choice is most often blood in the case of patients who have not undergone bone marrow transplantation in the past. Blood should be collected into a tube with an anti-clotting agent, preferably ethylenediaminetetraacetic acid (EDTA), and sent to an appropriate laboratory at room temperature or gently chilled (to 4 °C).

How should the results of *MEN1* genetic testing be read?

The report of *MEN1* testing will typically inform about the method used for analysis and any identified variants and will preferably also provide the physician with a brief comment about how to interpret the findings in clinics. However, the type and amount of information given may differ, depending on the laboratory.

First-line laboratory testing consists of the analysis of the *MEN1* gene sequence, usually by means of DNA sequencing (Sanger or high-throughput), which is sometimes preceded by high-resolution melting analysis (HRM). The result will typically be presented at the DNA and protein level. There are no specific hotspot regions in the *MEN1* gene, which would be preferentially mutated; therefore, a large number of the detected variants are family-specific and must be interpreted on an individual basis. Any changes in the *MEN1* gene that will impact protein length, structure, or function are very likely to have a deleterious clinical effect but still need to be looked up in appropriate databases and/or analyzed by bioinformatics tools to deduce their clinical interpretation. Clinically, a variant may be assigned as benign or likely benign, which means that it also appears in the general population and is (likely) not causative of MEN1. A pathogenic or likely pathogenic variant means that there is evidence that the detected alteration causes clinical features of MEN1. The most problematic interpretation is that of so-called variants of unknown/uncertain significance (VUS), which means that there is conflicting evidence regarding the pathogenicity of the given variant. In the case of genes with no mutation hotspot regions, as it is the case with the *MEN1* gene, many of the detected allelic variants may be VUSes. Sequencing analysis will identify a (likely) pathogenic variant in the *MEN1* gene in up to 90% of all MEN1 patients. If no potentially causative variant in the sequence is detected, the second line of laboratory testing may

be performed, which is deletion analysis. Large deletions (e.g., encompassing a whole exon or even the whole gene) are not identified by most sequencing analyses but may be present in 1–4% of all MEN1 cases. These kinds of alterations are identified by methods like quantitative PCR, multiplex ligation-dependent probe amplification (MLPA), or chromosomal microarrays. The results obtained for the patient should be interpreted collectively, that is, if any among pathogenic sequence variants and/or large deletion are present in a patient, this would confirm MEN1 diagnosis.

What if genetic testing is negative (no pathogenic variant has been detected) in a patient with MEN1 phenotype?

First of all, it should be made sure that not only the sequence of the *MEN1* gene has been analyzed but that also deletion testing has been performed. Some laboratories may do this at once, but others may not, and it will be necessary to ask for this additional testing. If, however, there is a negative result (no pathogenic alteration) in both sequence and deletion analysis, but the patient and/or his/her family is clinically strongly indicative of MEN1, the presence of a very rare syndrome called MEN4 (multiple endocrine neoplasia type 4) may be suspected. Clinically, MEN4 and MEN1 may be indistinguishable from one another at most stages. However, MEN4 is caused by mutations in another gene, *CDKN1B*, the variants of which are identified in an additional genetic test.

What is phenocopy?

The term phenocopy represents the phenomenon when the clinical picture associated with a genetic disease is caused by another background. As discussed in the preceding question–answer pair, MEN4 can be a MEN1 phenocopy. Moreover, another possibility of MEN1 phenocopy is related to the association of sporadic tumors mimicking the tumor associations in MEN1. Since both primary hyperparathyroidism and pituitary adenoma are rather frequent diseases, their association might raise the clinical suspicion of MEN1. Genetic testing is needed to rule out phenocopy.

Which routine laboratory test can be used to make the diagnosis of MEN1 unlikely in elderly patients?

Since the penetrance of primary hyperparathyroidism in MEN1 is almost 100% over the age of 50, a normal serum calcium in elderly patients makes the diagnosis of MEN1 unlikely. Certainly, if the suspicion is strong, genetic testing should be performed.

What are the recommended diagnostic procedures in patients with diagnosed MEN1 syndrome?

Patients with two or more tumors typical for MEN1 should be actively monitored for the presence of other tumors, even if clinically silent. If the screening results are negative, biochemical and radiological reevaluation should be performed on a regular basis.

In our case, clinical, biochemical, and radiological confirmation of insulinoma, hyperparathyroidism, and prolactinoma was established. Thorough physical examination of the skin revealed collagenomas, which are the atypical skin lesions accompanying MEN1 syndrome (Fig. 50.7).

How should we treat a patient with the MEN1 syndrome?

The choice of treatment depends on the clinical presentation. In case of our patient with insulinoma and symptomatic hypoglycemia, pharmacological treatment of hyperinsulinemia with diazoxide was primarily introduced. The clinically stable patient underwent surgical resection of the pancreatic lesion.

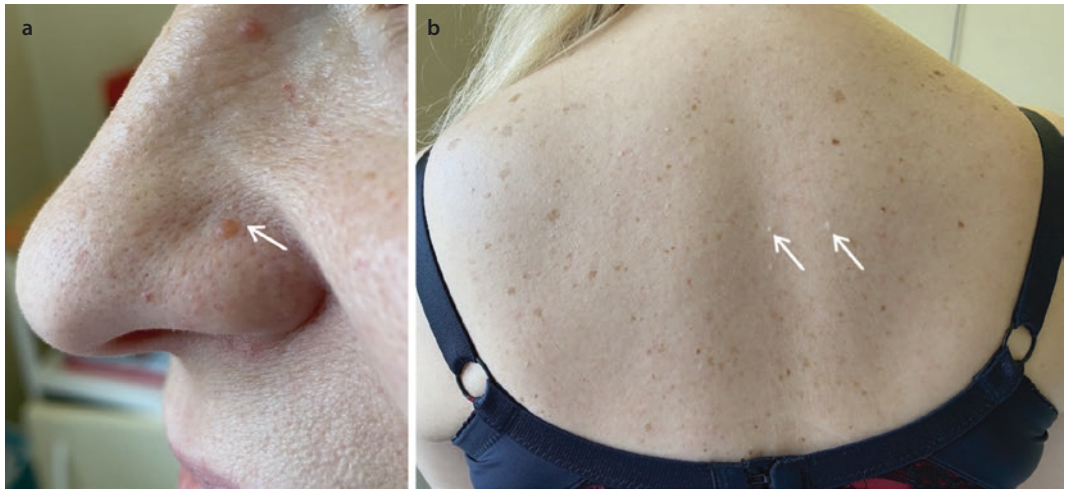

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Fig. 50.7 Collagenomas (indicated with arrows)—one of MEN1 syndrome skin manifestations

The management of choice for parathyroid adenomas is surgical resection of overactive glands. In MEN1 syndrome, either subtotal or total parathyroidectomy is advised. However, it must be taken into consideration that MEN1 is associated with an increased risk of persistent or recurrent hypercalcemia after subtotal surgery, which is thought to be secondary to the tendency toward multiglandular disease. In case of total parathyroidectomy, some centers implant a small parathyroid tissue autograft into the forearm (or in the neck) to avoid hypoparathyroidism and the autograft can be easily removed if primary hyperparathyroidism recurs.

The patient underwent subtotal parathyroidectomy with confirmatory pathological examination. Biochemical screening for primary hyperparathyroidism in patients with MEN1 should be performed annually with the assessment of serum calcium and parathyroid hormone concentrations.

In the case of prolactinomas, unlike other subtypes of pituitary adenomas, pharmacological treatment with dopamine agonists is the modality of choice. Neurosurgery is reserved for patients not responsive to medical treatment and/or with macroadenomas with local tumor mass symptoms. In our patient with confirmed microadenoma, cabergoline was effective in decreasing prolactin concentrations as well as tumor shrinkage observed in the follow-up MRI.

What features and symptoms in the family members raise the suspicion of MEN1? Should we screen the family members in case of negative results?

In our case the patient's two relatives (father and one sister) had a long history of nephrolithiasis which could be associated with primary hyperparathyroidism. The sudden death of the father at the age of 48 due to pituitary apoplexy was probably the first manifestation of macroadenoma.

The familial screening in MEN1 syndrome includes the regular clinical and biochemical assessment of the asymptomatic first-degree relatives of a patient diagnosed with MEN1. In the case of negative results, the biochemical and radiological screening should be repeated annually. Once any MEN1-related tumor is diagnosed, they should undergo the same screening procedures as patients with confirmed pathogenic *MEN1* variants.

Is it reasonable to perform genetic testing for *MEN1* variants in unaffected family members of a MEN1 patient?

Genetic testing in unaffected family members makes sense only if a causative genetic alteration has been detected in at least one of their affected first-degree relatives. In such a case, the genetic analysis of the unaffected person is limited down to the region in which the familial variant would be expected.

The detection of a pathogenic genetic variant in *MEN1* confirms the diagnosis of MEN1, even in the absence of clinical manifestations. The overall penetrance for clinical features of MEN1 is over 95% by age 40 years, which means that by the age of 40 years, the disease will present clinically in more than 95% of *MEN1* pathogenic variant-carriers. Therefore, it seems reasonable to offer genetic analyses also to unaffected family members, as this allows to implement additional clinical screening strategies in yet asymptomatic patients with a mutated *MEN1* gene.

Is it possible to predict the patient's outcome based on the results of genetic testing?

No, genetic testing can only confirm or exclude the presence of MEN1 in MEN1-suspected patients or the predisposition to MEN1 in unaffected family members. However, even among patients from the same family, whose disease is caused by the same mutation in the *MEN1* gene, the clinical outcome may differ significantly in means of the age of onset, disease symptoms, its dynamics, overall prognosis, and so on.

Genetic testing for MEN1 can be indicated in which forms of sporadic tumors?

A significant portion of some rare tumors arise in the context of MEN1. About 25% of gastrinomas are MEN1-related; therefore, genetic testing for MEN1 is indicated for patients with gastrinoma. On the other hand, a much less proportion of sporadic insulinoma is MEN1-related. Primary hyperparathyroidism is mostly sporadic; however, parathyroid adenoma in young patients (<30 years) or multiple parathyroid tumors might also indicate testing for MEN1.

Tips

The reader is advised to read the chapters on pituitary tumors prolactinoma (▶ Chap. 1), acromegaly (▶ Chap. 2), Cushing's disease and non-functional pituitary adenoma (▶ Chaps. 3 and 4), primary hyperparathyroidism (▶ Chap. 22), insulinoma (▶ Chap. 46), gastrinoma (▶ Chap. 48), and also the next chapter on the other major form of multiple endocrine neoplasia (MEN2) (▶ Chap. 51).

Take Home Messages

- Multiple endocrine neoplasia type 1 is a rare disease leading to serious morbidity.
- The suspicion for the disease can be raised based on the characteristic clinical symptoms and biochemical, hormonal, and imaging results.
- Diagnosis of two or more tumors typical for MEN1 syndrome implies the need to search for other tumors. If not found, the screening should be repeated in certain time intervals.
- Genetic screening should be offered to the patient and the family of the patient.
- The family of the patient with diagnosed MEN1 syndrome should be screened for typical MEN1 features. If the screening is negative, it should be repeated in certain time intervals, even in children.

Suggested Reading

1. de Laat JM, van der Luijt RB, Pieterman CRC, et al. MEN1 redefined, a clinical comparison of mutation-positive and mutation-negative patients. BMC Med. 2016;14(1):182. https://doi.org/10.1186/s12916-016-0708-1, indexed in Pubmed: 27842554.
2. KMa D, CJm L. Diagnosis and Management of Multiple Endocrine Neoplasia Type 1 (MEN1). Hered Cancer Clin Pract. 2005;3(1):1–6. https://doi.org/10.1186/1897-4287-3-1-1.
3. Ito T, Igarashi H, Uehara H, et al. Causes of death and prognostic factors in multiple endocrine neoplasia type 1: a prospective study: comparison of 106 MEN1/Zollinger-Ellison syndrome patients with 1613 literature MEN1 patients with or without pancreatic endocrine tumors. Medicine (Baltimore). 2013;92(3):135–81. https://doi.org/10.1097/MD.0b013e3182954af1.
4. Marini F, Falchetti A, Del Monte F, et al. Multiple endocrine neoplasia type 1. Orphanet J Rare Dis. 2006;1:38. https://doi.org/10.1186/1750-1172-1-38.
5. Thakker RV, Newey PJ, Walls GV, et al. Endocrine Society. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab. 2012;97(9):2990–3011. https://doi.org/10.1210/jc.2012-1230.
6. van Beek D-J, et al. 'Quality in, quality out', a stepwise approach to evidence-based medicine for rare diseases promoted by multiple endocrine neoplasia type 1. Endocr Connect. 2018;7(11):R260–74. Endocr Connect. 2018; 7(11):R260–R274. https://doi.org/10.1530/EC-18-0359.
7. van Leeuwaarde RS, de Laat JM, Pieterman CRC, et al. The future: medical advances in MEN1 therapeutic approaches and management strategies. Endocr Relat Cancer. 2017;24(10):T179–93. https://doi.org/10.1530/ERC-17-0225.
8. Yates CJ, Newey PJ, Thakker RV. Challenges and controversies in management of pancreatic neuroendocrine tumors in patients with MEN1. Lancet Diabetes Endocrinol. 2015;3(11):895–905. https://doi.org/10.1016/S2213-8587(15)00043-1.

Multiple Endocrine Neoplasia Type 2

Peter Igaz

Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_51

Opening

Multiple endocrine neoplasia type 2 (MEN2) syndrome is a rare, hereditary tumor syndrome predisposing affected patients to multiple tumors including medullary thyroid cancer, pheochromocytoma, and primary hyperparathyroidism.

Definition of the Disease

The MEN2 syndrome is a rare disease with a prevalence of 1:30.000. It is inherited as an autosomal dominant trait and is caused by mutations of the protooncogene *RET* (rearranged upon transfection). Its major features include medullary thyroid cancer (MTC) and pheochromocytoma. There are two major subtypes of MEN2 (■ Table 51.1). MEN2A (Sipple syndrome) patients are affected by MTC, pheochromocytoma, and parathyroid tumors resulting in primary hyperparathyroidism. MEN2B (Gorlin syndrome) is a very rare form with poor prognosis associated with very aggressive MTC and pheochromocytoma, and characteristic phenotypical signs such as marfanoid appearance, mucosal neuroma, and intestinal ganglioneuromatosis. Previously, a third form was classified as FMTC (familial medullary thyroid cancer) only associated with MTC (without pheochromocytoma and hyperparathyroidism), but nowadays it is considered as an MEN2A variant.

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Case Presentation

A 31-year-old man was referred to our Department with a right adrenal mass of 5 cm diameter (ultrasound and computed tomography (CT)). He had repeated episodes of chest pains, palpitation, and pallor in the past 2 years. He had blood pressure as high as 270/150 mmHg during these attacks.

What is the most probable diagnosis?

Based on the symptoms and the adrenal mass, an adrenal pheochromocytoma can be suspected (▶ Chap. 37).

How to proceed?

The hormonal activity of the tumor should be confirmed. Catecholamine metabolites should be investigated. Urinary catecholamine metabolites were highly elevated (metanephrine: 3645 µg/24 h (normal: 64–302); normetanephrine: 895 µg/24 h (normal: 162–157)), and serum chromogranin A level was also increased (249.7 ng/ml – normal <98.1). Due to the life-threatening elevations of blood pressure, after careful preparation (introduction of alpha-adrenergic, then beta-receptor blockers), a laparoscopic right adrenalectomy was performed, and the histology confirmed pheochromocytoma.

Should a hereditary disease be looked for?

Recent findings show that at least 40% of Pentagastrin is injected intravenously 50% of pheochromocytomas may develop as manifestations of autosomal dominantly inherited hereditary tumor syndromes caused by germline mutations (see ▶ Chap. 37 on pheochromocytoma). In case of adrenal pheochromocytomas, MEN2 syndrome, von Hippel-Lindau syndrome (VHL syndrome) and neurofibromatosis type 1 (NF1) should be considered, but mutations in succinate dehydrogenase (SDH) genes, and in other more recently described genes such as *TMEM127* might also be pathogenic.

Bilateral pheochromocytomas are most often caused by VHL and MEN2 syndromes.

Which patients suffering from pheochromocytoma should be screened for genetic background?

Given the high proportion of pheochromocytomas occurring in hereditary tumor syn-

Table 51.1 Main forms of the MEN2 syndrome

	Subtypes	Manifestations	Percentage
MEN2A	Classical	Medullary thyroid cancer	95–100%
		Pheochromocytoma	40–50%
		Primary hyperparathyroidism	20–30%
	FMTC	Medullary thyroid cancer	~100%
	MEN2A with cutaneous lichen amyloidosis		
	MEN2A with Hirschsprung disease		
MEN2B		Medullary thyroid cancer	100%
		Pheochromocytoma	50%
		Marfanoid appearance, mucosal neuromas, corneal nerve hypertrophy, intestinal ganglioneuromatosis	

FMTC familial medullary thyroid cancer

dromes, all patients with pheochromocytoma can be proposed to have genetic screening. Special circumstances, for example, young patients (<50 years), bilateral tumors, children, extraadrenal pheochromocytoma, metastatic pheochromocytoma, and the presence of other endocrine (or non-endocrine) tumors increase the likelihood of hereditary disease; therefore in these cases genetic screening is absolutely warranted.

Which clues could help us in the quest for a hereditary disease?

Other manifestations of the VHL syndrome include cerebellar and retinal hemangiomas, renal cancer and cysts, pancreatic cysts and neuroendocrine tumors, and epididymis cystadenomas. As the most penetrant manifestation of MEN2 is medullary thyroid cancer, calcitonin should be taken as a tumor marker and a thyroid ultrasound should also be undertaken. Neurofibromatosis type 1 is associated with characteristic skin manifestations including café-au-lait spots (Fig. 51.1), neurofibromas (soft, usually light brown skin tumors), and characteristic ophthalmological lesions (Lisch-nodules, i.e., hamartomas of the iris).

A careful physical examination and history taking including the family is always warranted, and this could help is in guiding the order genetic investigations, that is which genes should be sequenced first.

Case Presentation Continued…

Calcitonin was slightly elevated (29 pg/ml – normal <6 pg/ml). Ultrasound of the thyroid showed two small lesions of 4x4x5 and 4x4x6 mm in the left and right lobes, respectively. Fine needle aspiration biopsy confirmed medullary thyroid cancer from both lesions. Carcinoembryonic antigen (CEA) that is also a tumor marker for MTC was mildly elevated, as well (6.2 ng/ml; normal <4 ng/ml).

Serum calcium and parathyroid hormone should also be measured, as MEN2A syndrome also can include primary hyperparathyroidism. These were, however, normal.

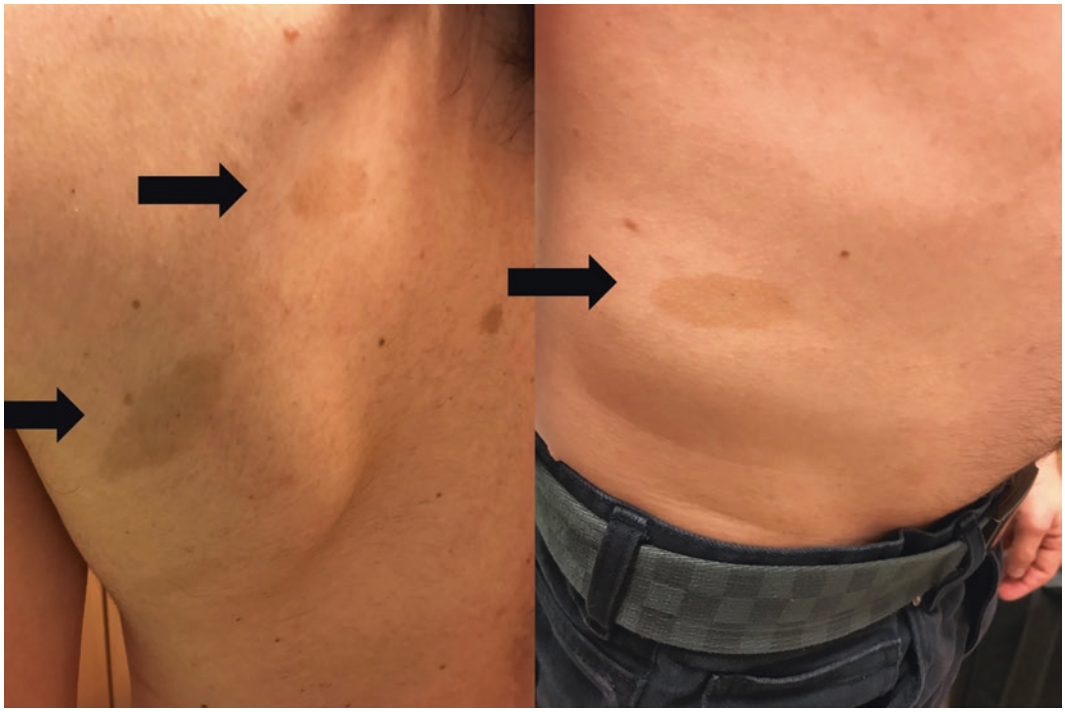

Fig. 51.1 Typical café-au-lait spot in a patient with neurofibromatosis type 1

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How to proceed?

Total thyroidectomy was performed, and histology confirmed the diagnosis of MTC in both lobes. Clinically, the diagnosis of MEN2 syndrome could be established based on the presence of both an MTC and a pheochromocytoma in the same individual. Genetic diagnosis was performed using DNA isolated from peripheral blood, and sequencing of the *RET* protooncogene exons known to harbor MEN2-causing mutations was performed. A common missense mutation in exon 11 of *RET* was found (Codon 634, TGC634TGG leading to a Cysteine-Tryptophan change).

Mutations of codon 634 are found in approximately 80% of MEN2A patients, and there are strong genotype-phenotype correlations, that is certain mutations are associated with distinct clinical manifestations.

How could the molecular pathogenesis of MEN2 be briefly summarized?

Mutations of the *RET* (rearranged upon transfection) gene are responsible for MEN2. This gene is considered as a protooncogene and codes for a cell surface receptor that is a receptor tyrosine kinase. The ligands of the *RET* protein belong to the GDNF family (glial cell-derived neurotrophic factors) and these are important in the development of the nervous system. Mutations mostly lead to the ligand-independent activation of the receptor (e.g., by promoting receptor dimerization, or by directly inducing catalytic activity of the intracellular kinase domain that is characteristic for exon 16 mutation in MEN2B). Mutations are mostly missense, that is amino acid changes that activate the protein (activating mutations). The *RET* gene has 21 exons, but not all of these were found to harbor mutations. There are mutation hot spots where mutations are mostly found to occur (exons 11, 10, 8, 9, 14 in MEN2A and exon 16 (rarely exon 15) in MEN2B).

Being a hereditary disease, family screening should be performed.

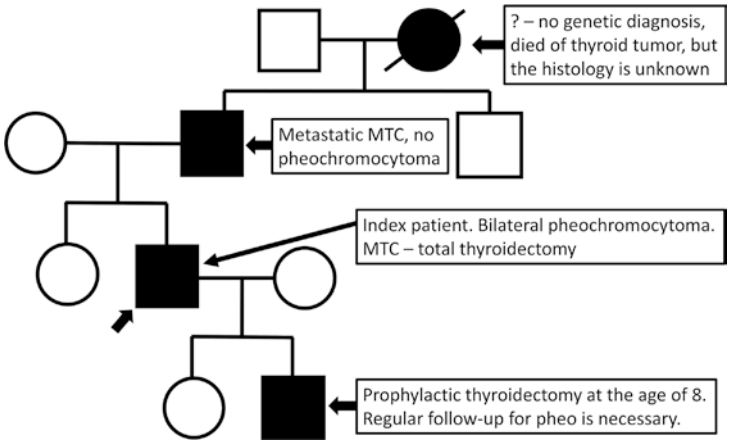

Fig. 51.2 Family tree of the patient with MEN2A. Note that affected patients are found in every generation characteristic for an autosomal dominantly inherited trait. Circles: women, squares: men, affected patients are black, the index patient is indicated by an arrow

The family tree of the patients is shown in Fig. 51.2. The father of the patient and his 8-year-old son were found to have the same mutation. The father was diagnosed with metastatic MTC, but no signs of pheochromocytoma or primary hyperparathyroidism were found. A total thyroidectomy was performed, but calcitonin levels remained elevated after surgery and multiple metastases were confirmed. He refused further treatment.

What should be done with the mutation carrier son?

As *RET* mutation carriers have an almost 100% chance to develop MTC, prophylactic thyroidectomy should be performed. The timing of surgery depends on the type of *RET* mutation, as there are strong genotype-phenotype correlations known in MEN2. In carriers with mutations associated with the highest risk for MTC, that is codon 918 (exon 16) mutations associated with MEN2B, the thyroidectomy should be performed during the first year of life. In high-risk mutation carriers (e.g., codons 634 and 883), the operation should be performed before the age of five. The timing of surgery is not defined for carriers of other mutations conveying moderate risk (e.g., codons 609, 611 in exon 10, or exon 14 mutations, etc.). These patients should be operated as children or young adults, but there are reports of some low-risk mutations whose carriers do not have MTC even in the fourth or fifth decades of life. In these patients, regular calcitonin measurements and/or pentagastrin tests (if available) can be performed, and operation is warranted following the first pathological results.

What is pentagastrin and what is it used for?

Pentagastrin includes the five C-terminal amino acids of gastrin and it is a potent stimulus of calcitonin release and thereby can be used for the screening for MTC or C-cell hyperplasia. Pentagastrin is injected intravenously over 3 minutes (at a dose of 0.5 μg/kg body weight) and blood is taken 2 and 5 minutes thereafter. If the calcitonin rises over 200 ng/ml, MTC diagnosis is very likely, whereas values <100 ng/ml are not suspicious for MTC. The range between 100 and 200 ng/ml is uncertain. Alternatively, intravenous calcium can be used (2.5 mg Ca/kg body weight) injected over 30 seconds.

Why not to perform prophylactic adrenalectomy?

If prophylactic thyroidectomy is indicated, the question might be raised why prophylactic bilateral adrenalectomy is not. You might argue that pheochromocytoma is also a life-threatening condition. However, the chance for pheochromocytoma is only about 50%, whereas that of MTC is almost

100% in MEN2. Pheochromocytoma is mostly benign in MEN2. Moreover, thyroid hormone substitution is rather easy with a fixed dose, whereas the substitution of adrenocortical hormones is not, and hydrocortisone doses should be increased during stress situations (infections, trauma, surgery, etc.) (▶ Chap. 31 on Addison's disease).

How should the patient be followed-up?

Calcitonin and serum calcium should be regularly measured (e.g., every 6 months or year). Catecholamine metabolites should also be examined yearly even after bilateral adrenalectomy. Five years after the removal of the right adrenal, a mild elevation of urinary metanephrines was observed (540 µg/24 h – normal 64–302) and CT showed a discrete mass of 2 cm diameter in the left adrenal. ^{123}I-MIBG scintigraphy showed isotope accumulation in the lesion. Even if the tumor was small and the patient's hypertension could be well-controlled by a calcium antagonist (amlodipine), based on the genetic background and the potential long-term deterioration of the clinical situation, a left adrenalectomy was also performed. Histology confirmed pheochromocytoma. Hydrocortisone and fludrocortisone substitution were started.

What kind of other variants of the MEN2A syndrome are known?

FMTC patients have only MTC as a MEN2 manifestation. To establish the diagnosis of familial FMTC, ten affected patients without other manifestations should be found in the same family.

MEN2A with cutaneous lichen amyloidosis is a form where papular and pigmented skin lesions are observed mostly on the extensor sides of the extremities and in the interscapular regions.

MEN2A associated with Hirschsprung disease is a syndrome that is very interesting from a scientific point of view. Hirschsprung disease is a congenital disease characterized by the absence of autonomic ganglion cells leading to intestinal obstruction and megacolon. A part of Hirschsprung disease is caused by *RET* mutations, but in contrast to MEN2, these are inactivating (with reduced protein function). In MEN2A associated with Hirschsprung, the same *RET* mutation (mostly in codon 620) results in tumor formation in the C-cells of thyroid as an activating, and Hirschsprung disease as an inactivating mutation. How could this be possible? The answer may lie in the different activity of the *RET* protein in the enteric nervous system and the organs affected by tumors.

What are the features of the MEN2B syndrome?

MEN2B is associated with a very aggressive form of MTC that was reported to metastatize even in children less than 1 year of age. Prophylactic thyroidectomy should therefore be performed in carriers of *RET* mutations predisposing to MEN2B during the first year of life. Due to the aggressivity of MEN2B, the syndrome is mostly sporadic. Apart from MTC and pheochromocytoma (Table 51.1), MEN2B patients have typical phenotypic features including mucosal neuroma on the lips (Fig. 51.3b), on the tongue (Fig. 51.3c). Intestinal ganglioneuromatosis can lead to chronic obstipation and megacolon (Fig. 51.4). Note that megacolon can also occur in MEN2A in its subtype associated with Hirschprung disease, but the pathogenesis of this is completely different (ganglioneuromatosis leading to obstruction in MEN2B vs. aganglionosis in Hirschsprung disease). Marfanoid appearance, kyphoscoliosis (Fig. 51.3a), joint laxity, and corneal nerve hypertrophy can also be observed. In contrast with Marfan syndrome, however, aortic abnormalities are not observed.

What are the main differences between MEN1 and MEN2 syndromes?

Table 51.2 compares some important features of these two tumor syndromes.

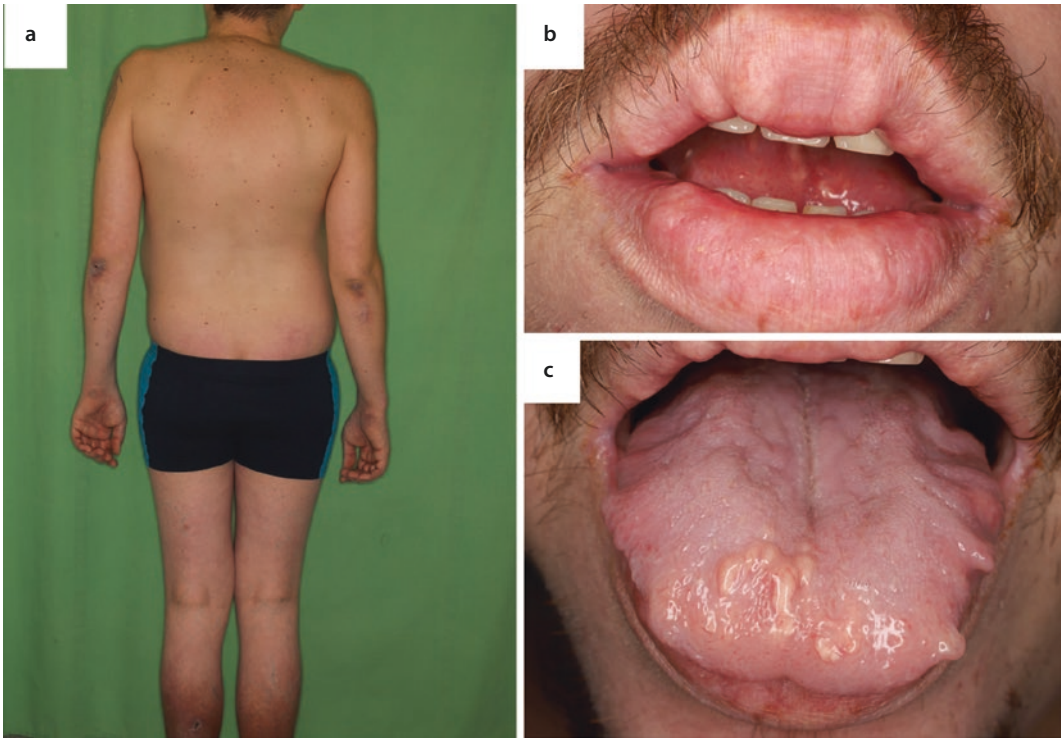

Fig. 51.3 Typical features of a patient suffering from MEN2B. **a** Kyphoscoliosis. **b** Neuromas on the lips. **c** Neuromas on the tongue. (Courtesy of Dr. Géza Nagy, 2nd Department of Internal Medicine, Semmelweis University)

Is testing for MEN2 warranted in patients with medullary thyroid cancer?

Medullary thyroid cancer is a rare, non-differentiated form of thyroid cancer. About 20–30% of medullary thyroid cancer arises in the context of MEN2, and therefore routine genetic testing for germline *RET* mutations can be proposed even in sporadic MTC. The chance to find MEN2 is greater in younger MTC patients, but there are reports on positive genetic findings even in elderly MTC patients.

Tips

The reader is advised to read the chapters on medullary thyroid cancer (▶ Chap. 19), primary hyperparathyroidism (▶ Chap. 22), pheochromocytoma (▶ Chap. 37), and the next chapter on von Hippel-Lindau syndrome (▶ Chap. 52).

Take Home Messages

- Multiple endocrine neoplasia type 2 (MEN2) is a rare, autosomal dominantly inherited tumor syndrome having two main subtypes, MEN2A and MEN2B.
- Major manifestations of MEN2A include medullary thyroid cancer (MTC), pheochromocytoma, and primary hyperparathyroidism, whereas MEN2B is associated with an aggressive form of MTC and pheochromocytoma along with characteristic phenotypic features (mucosal neuroma, marfanoid appearance, and intestinal ganglioneuromatosis).
- MEN2 is caused by mutations of the *RET* protooncogene, and there are strong genotype-phenotype correlations known.
- Prophylactic thyroidectomy should be performed in carriers of *RET* protooncogene mutations predisposing to MEN2, and the timing of surgery is influenced by the mutation type.

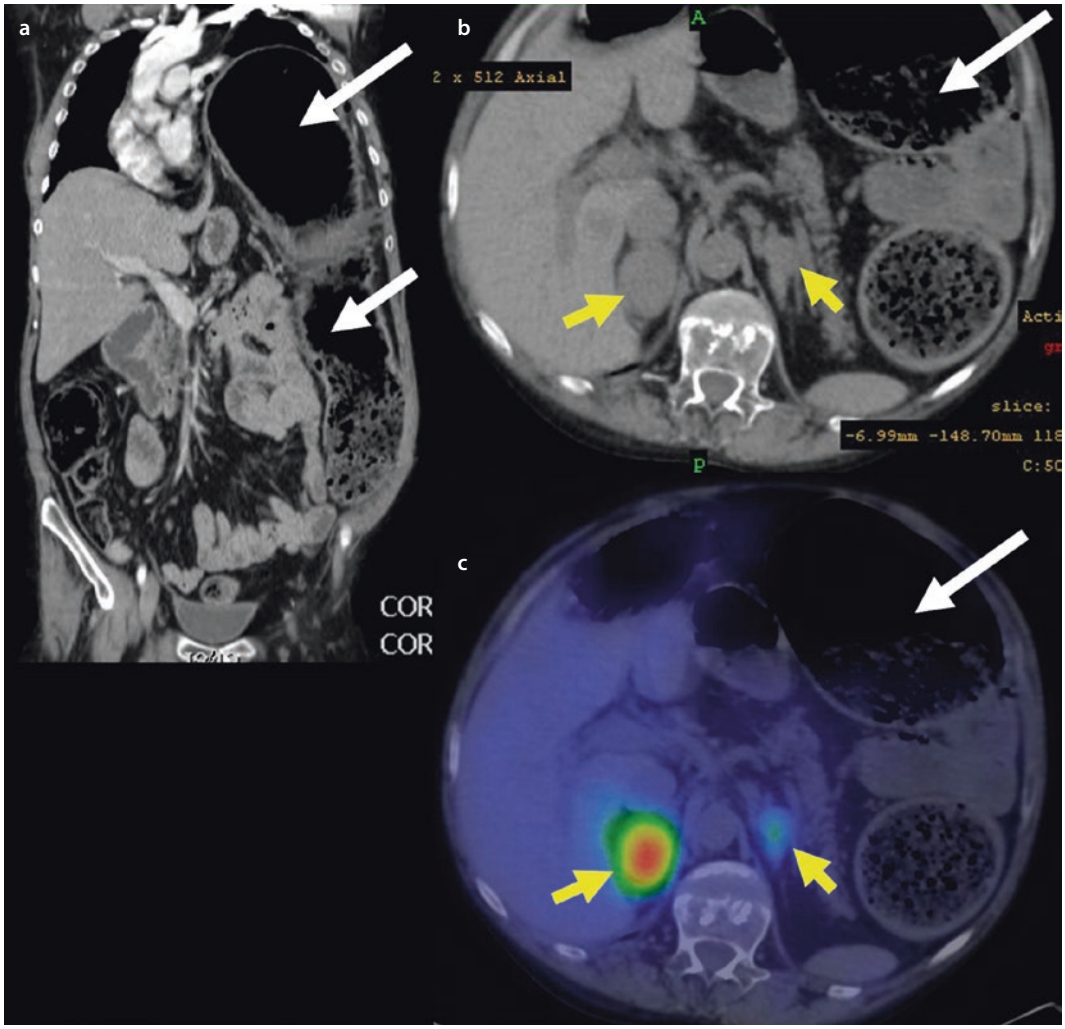

Fig. 51.4 **a** Megacolon due to obstruction caused by intestinal ganglioneuromatosis in a MEN2B patient (white arrows), coronal CT picture. A part of the megacolon is herniated to the thorax. **b** Axial CT-imaging of a bilateral pheochromocytoma in MEN2B (yellow arrows). **c** ^{123}I-MIBG scintigraphy-SPECT-CT imaging of bilateral pheochromocytoma in MEN2B. (Courtesy of Dr. Géza Nagy, 2nd Department of Internal Medicine, Semmelweis University)

Table 51.2 Comparison of the MEN1 and MEN2 syndromes

	MEN1	MEN2
Inheritance	Autosomal dominant	Autosomal dominant
Function of the disease-causing gene	Tumor suppressor	Protooncogene
Mutation hotspots in the gene	No	Yes
Most penetrant manifestation	Hyperparathyroidism	Medullary thyroid cancer
Genotype-phenotype correlations	–	Strong
Prophylactic operation	–[a]	Prophylactic thyroidectomy

[a]There is no routine prophylactic operation in MEN1 except for performing thymectomy during operation for hyperparathyroidism. Penetrance shows the chance of a phenotypic alteration to occur based on a genotype. Both hyperparathyroidism in MEN1 and medullary thyroid cancer in MEN2 have almost 100% penetrance meaning that almost every individual carrying a mutated gene will have the clinical manifestation

Suggested Reading

1. Brandi ML, Gagel RF, Angeli A, Bilezikian JP, Beck-Peccoz P, Bordi C, Conte-Devolx B, Falchetti A, Gheri RG, Libroia A, Lips CJ, Lombardi G, Mannelli M, Pacini F, Ponder BA, Raue F, Skogseid B, Tamburrano G, Thakker RV, Thompson NW, Tomassetti P, Tonelli F, Wells SA Jr, Marx SJ. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab. 2001;86(12):5658–71. https://doi.org/10.1210/jcem.86.12.8070.
2. Decmann A, Patocs A, Igaz P. Overview of genetically determined diseases/multiple endocrine neoplasia syndromes predisposing to endocrine tumors. Experientia Suppl. 2019;111:105–27. https://doi.org/10.1007/978-3-030-25905-1_7.
3. Larouche V, Akirov A, Thomas CM, Krzyzanowska MK, Ezzat S. A primer on the genetics of medullary thyroid cancer. Curr Oncol. 2019;26(6):389–94. https://doi.org/10.3747/co.26.5553.
4. Moore SW, Zaahl M. The Hirschsprung's-multiple endocrine neoplasia connection. Clinics (Sao Paulo, Brazil). 2012;67(Suppl 1):63–7. https://doi.org/10.6061/clinics/2012(sup01)12.
5. Mucha L, Leidig-Bruckner G, Frank-Raue K, Bruckner T, Kroiss M, Raue F. Phaeochromocytoma in multiple endocrine neoplasia type 2: RET codon-specific penetrance and changes in management during the last four decades. Clin Endocrinol. 2017;87(4):320–6. https://doi.org/10.1111/cen.13386.
6. Raue F, Frank-Raue K. Update on multiple endocrine neoplasia type 2: focus on medullary thyroid carcinoma. J Endoc Soc. 2018;2(8):933–43. https://doi.org/10.1210/js.2018-00178.
7. Wells SA Jr, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, Lee N, Machens A, Moley JF, Pacini F, Raue F, Frank-Raue K, Robinson B, Rosenthal MS, Santoro M, Schlumberger M, Shah M, Waguespack SG. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid. 2015;25(6):567–610. https://doi.org/10.1089/thy.2014.0335.
8. Wells SA Jr. Advances in the management of MEN2: from improved surgical and medical treatment to novel kinase inhibitors. Endocr Relat Cancer. 2018;25(2):T1–t13. https://doi.org/10.1530/erc-17-0325.

Von Hippel–Lindau Syndrome

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Contents

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0_52

Opening

Von Hippel–Lindau syndrome (VHL-syndrome) is a rare hereditary tumor syndrome predisposing affected patients to hemangioblastomas in the central nervous system (CNS) and retina, kidney cancer and also to neuroendocrine tumors including pheochromocytoma and pancreatic neuroendocrine tumors.

Definition of the Disease

The VHL-syndrome is a rare tumor syndrome (prevalence: 1:36,000) inherited as an autosomal dominant trait. The syndrome is caused by germ-line mutations in the tumor suppressor VHL-gene. The major manifestations of the VHL-syndrome include hemangioblastomas in the central nervous system (mostly in the spinal cord and cerebellum) and retina (retinal angioma), renal cysts and clear cell renal carcinoma, endolymphatic sac tumors of the middle ear, cysts, serous cystadenomas and neuroendocrine tumors in the pancreas, and cystadenomas of the epididymis. There are two major subtypes of VHL (Table 52.1): in VHL type 1, there is usually no pheochromocytoma/paraganglioma, whereas in type 2 pheochromocytoma/paraganglioma can develop. The only manifestation in VHL type 2C is pheochromocytoma that is often bilateral. The risk for renal cancer is low in VHL type 2A and high in type 2B. Patients suffering from VHL usually die due to complications related to central nervous system tumors and renal cell cancer. Pheochromocytoma or rarely paraganglioma is observed in 10–30% of VHL-syndrome patients, and as these tumors secrete predominantly norepinephrine, the typical symptoms of pheochromocytoma are lacking. Pheochromocytoma in VHL is rarely metastatic. In sporadic cases, VHL-syndrome is often diagnosed due to central nervous system manifestations.

The pathogenesis of VHL-syndrome is related to the activation of hypoxia-inducible factor 1α that stimulates angiogenesis and the product of VHL-gene is implicated in its degradation. Due to the increased angiogenesis, tumors are usually highly vascularized.

Case Presentation

The male patient complained of serious dizziness at the age of 22, and brain magnetic resonance imaging (MRI) revealed a cerebellar tumor. The tumor could be removed, and its histological examination revealed a hemangioblastoma. Four years later, a control MRI revealed a recurrent cerebellar tumor of 4 × 5 cm that was again successfully operated.

Table 52.1 Classification of the VHL-syndrome. Endocrine manifestations are highlighted in bold

VHL subtype		Manifestations
VHL type 1		Central nervous system hemangioblastoma, retinal angioma, renal cysts and cancer, endolymphatic sac tumor, *pancreatic* cysts and *neuroendocrine tumor*, epididymis cystadenoma
VHL type 2	2A	Central nervous system hemangioblastoma, retinal angioma, endolymphatic sac tumor, *pancreatic* cysts and *neuroendocrine tumor*, epididymis cystadenoma, *pheochromocytoma/paraganglioma*
	2B	Renal cysts and cancer, central nervous system hemangioblastoma, retinal angioma, renal cancer, endolymphatic sac tumor, *pancreatic* cysts and *neuroendocrine tumor*, epididymis cystadenoma, *pheochromocytoma/paraganglioma*
	2C	*Pheochromocytoma/paraganglioma*

Cerebellar hemangioblastoma (Lindau tumor) should wake the suspicion for von Hippel–Lindau syndrome. What should be done next?

Hemangioblastomas are uncommon tumors of the central nervous system, and these are important manifestations of the VHL-syndrome. About 40% of VHL-syndrome-associated hemangioblastomas occur in the cerebellum, whereas about 50% in the spinal cord.

A family tree should be taken to search for a potential hereditary case (Fig. 52.1 represents the patient's family tree), but the syndrome can occur sporadically as well. Genetic testing is mandatory. Careful history taking is important. Ophthalmological examination should be done for the potential retinal angiomas.

Genetic testing showed a heterozygous Glu94 STOP mutation in the first exon of the VHL-gene that is a known pathogenic mutation of the VHL-syndrome. What is the chance for passing this mutation to the offspring?

Being a heterozygous mutation, there is a 50% chance of passing it to the next generation. As VHL is inherited as an autosomal dominant trait, one mutant allele is enough for disease manifestation, and therefore, half of the offspring can be expected to manifest the disease.

What kind of imaging should be performed?

Abdominal imaging preferably by MRI (or computed tomography (CT)) should be done to investigate the kidneys, pancreas, and adrenals. The spine should be examined for potential spinal cord tumors.

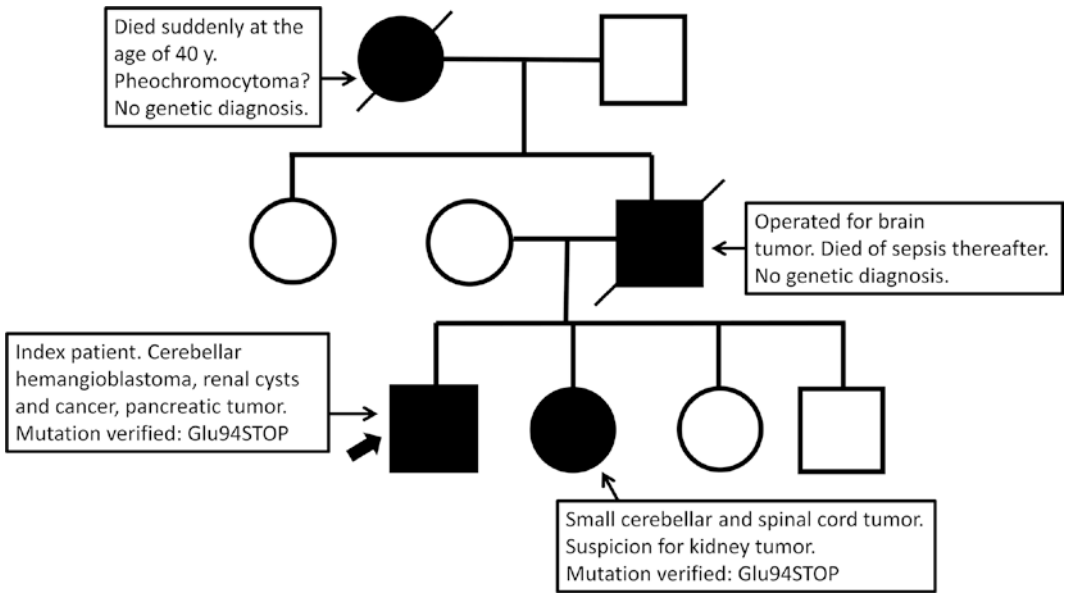

Fig. 52.1 Family tree of the patient. Note that affected patients are found in every generation characteristic for an autosomal dominantly inherited trait. Circles: women, squares: men, affected patients are black, the index patient is indicated by an arrow

Case Continued

Abdominal CT showed multiple cysts in the pancreas and the kidneys (Figs. 52.2a and b), but the adrenals were normal. In the left kidney, the suspicion for renal cancer was raised (solid tumor of 24 × 20 mm). A urological consultation was requested, but due to the small size (<3 cm diameter) of the tumor, only observation was proposed. A small lesion suspicious for tumor was described in the pancreas at the head-corpus boundary (Fig. 52.2a).

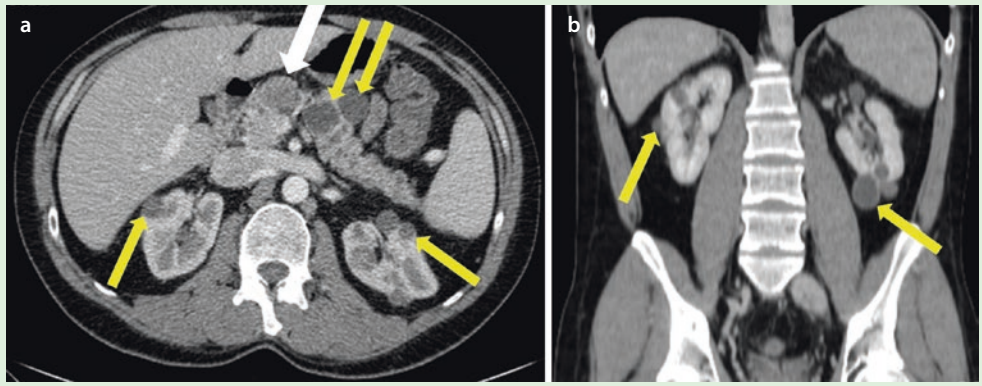

Fig. 52.2 **a** Axial abdominal CT image of the patient showing the pancreatic tumor (white arrow) at the pancreas head-corpus boundary and multiple cysts in the pancreas and both kidneys (yellow arrows). **b** Coronal CT image showing multiple kidney cysts (yellow arrows)

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Which hormones should be measured?

Pheochromocytoma/paraganglioma and pancreatic neuroendocrine tumors represent the endocrine manifestations of the VHL-syndrome. Urinary or plasma metanephrines (▶ Chap. 37) and chromogranin A (CgA) as the general neuroendocrine tumor marker should be taken (▶ Chap. 44). Pancreatic neuroendocrine tumors in VHL are usually hormonally inactive and indolent, but rarely can metastasize to the liver. All hormones measured were in the normal range.

Should the pancreas tumor be removed?

VHL is associated with neuroendocrine tumors in the pancreas that are usually slowly growing and indolent, and despite having metastatic potential, patients usually do not die of complications related to these. Tumors with a diameter under 3 cm should only be followed up.

Even for kidney tumors that have more serious clinical consequences than pancreatic neuroendocrine tumors in VHL, current clinical practice is rather conservative and aims to preserve as much normal kidney as possible. Kidney-sparing operations are preferred, and small tumors (<3 cm diameter) are usually only followed up.

How should the patient be followed up?

In patients older than 10 years of age, annual physical and ophthalmological examinations, abdominal ultrasound, and plasma/urinary metanephrines can be proposed. Abdominal, brain, and spine MRI should be performed every 2 years along with audiological control (for endolymphatic sac tumors of the middle ear).

Is there a medical treatment option available for VHL-syndrome?

There are reports on the successful use of the tyrosine kinase inhibitor sunitinib having anti-angiogenetic effects in patients suffering from VHL-syndrome. Increased angiogenesis is a major pathogenic feature of VHL-syndrome. Sunitinib is already in use for many years in the treatment of sporadic clear cell renal cancer, and it is also actively used in the treatment of differentiated pancreatic neuroendocrine tumors. Moreover, trials are ongoing for the use of sunitinib in metastatic pheochromocytoma.

Tips

The reader is advised to read the chapter on pheochromocytoma (▶ Chap. 37), the chapters on intestinal and pancreatic neuroendocrine tumors (▶ Chaps. 44, 46 and 48), and the previous chapter on MEN2 syndrome (▶ Chap. 51).

Take Home Messages

- Von Hippel–Lindau syndrome (VHL-syndrome) is a rare hereditary tumor syndrome inherited as an autosomal dominant trait.
- VHL-syndrome predisposes patients to central nervous system hemangioblastomas, retinal angiomas, renal cysts and cancer, pancreatic cysts and cystadenomas, endolymphatic sac tumors, and epididymis cystadenomas.
- Endocrine manifestations of VHL-syndrome include pheochromocytoma and pancreatic neuroendocrine tumors.
- VHL-patients usually die of complications associated with central nervous system hemangioblastomas and renal cancer. Pheochromocytoma is rarely metastatic, and pancreatic neuroendocrine tumors are usually indolent.

Suggested Reading

1. Bjorklund P, Pacak K, Crona J. Precision medicine in pheochromocytoma and paraganglioma: current and future concepts. J Intern Med. 2016;280(6):559–73. https://doi.org/10.1111/joim.12507.
2. Crespigio J, Berbel LCL, Dias MA, Berbel RF, Pereira SS, Pignatelli D, Mazzuco TL. Von Hippel-Lindau disease: a single gene, several hereditary tumors. J Endocrinol Investig. 2018;41(1):21–31. https://doi.org/10.1007/s40618-017-0683-1.
3. Neumann HP, Young WF Jr, Krauss T, Bayley JP, Schiavi F, Opocher G, Boedeker CC, Tirosh A, Castinetti F, Ruf J, Beltsevich D, Walz M, Groeben HT, von Dobschuetz E, Gimm O, Wohllk N, Pfeifer M, Lourenco DM Jr, Peczkowska M, Patocs A, Ngeow J, Makay O, Shah NS, Tischler A, Leijon H, Pennelli G, de Las Heras KVG, Links TP, Bausch B, Eng C. 65 Years of the double helix: genetics informs precision practice in the diagnosis and management of pheochromocytoma. Endoc Relat Cancer. 2018;25(8):T201–t219. https://doi.org/10.1530/erc-18-0085.
4. Nielsen SM, Rhodes L, Blanco I, Chung WK, Eng C, Maher ER, Richard S, Giles RH. Von Hippel-Lindau disease: genetics and role of genetic counseling in a multiple neoplasia syndrome. J Clin Oncol. 2016;34(18):2172–81. https://doi.org/10.1200/jco.2015.65.6140.
5. Oudard S, Elaidi R, Brizard M, Le Rest C, Caillet V, Deveaux S, Benoit G, Correas JM, Benoudiba F, David P, Gaudric A, Hammel P, Joly D, Timsit MO, Mejean A, Richard S. Sunitinib for the treatment of benign and malignant neoplasms from von Hippel-Lindau disease: a single-arm, prospective phase II clinical study from the PREDIR group. Oncotarget. 2016;7(51):85306–17. https://doi.org/10.18632/oncotarget.13301.
6. Sarkadi B, Patocs A. Hereditary diseases predisposing to pheochromocytoma (VHL, NF-1, paraganglioma syndromes, and novel genes). Experientia Suppl. 2019;111:129–47. https://doi.org/10.1007/978-3-030-25905-1_8.
7. Tsang SH, Sharma T. Von Hippel-Lindau disease. Adv Exp Med Biol. 2018;1085:201–3. https://doi.org/10.1007/978-3-319-95046-4_42.
8. Varshney N, Kebede AA, Owusu-Dapaah H, Lather J, Kaushik M, Bhullar JS. A review of Von Hippel-Lindau syndrome. J Kidney Cancer VHL. 2017;4(3):20–9. https://doi.org/10.15586/jkcvhl.2017.88.
9. Yuan G, Liu Q, Tong D, Liu G, Yi Y, Zhang J, Zhang Y, Wang LA, Wang L, Chen R, Guan Y, Yi X, Lan W, Jiang J. A retrospective case study of sunitinib treatment in three patients with Von Hippel-Lindau disease. Cancer Biol Ther. 2018;19(9):766–72. https://doi.org/10.1080/15384047.2018.1470732.

Supplementary Information

P. Igaz (ed.), *Practical Clinical Endocrinology*, https://doi.org/10.1007/978-3-030-62011-0

Appendix

- **Conventional (traditional), SI units and conversion factors for the most important hormones (conventional units should be multiplied by the conversion factor to get the SI Units)**

SI: Système International

	Conventional units	Conversion factor to SI	SI units
Pituitary hormones			
Prolactin	ng/mL	20	mIU/L
	ng/mL	0.043	nmol/L
GH	ng/mL	46.5	pmol/L
IGF-1	ng/mL = µg/L	0.13	nmol/L
TSH	µIU/mL	1	mIU/L
ACTH	pg/mL	0.22	pmol/L
FSH	mU/mL	1	IU/L
LH	mU/mL	1	IU/L
Thyroid			
fT4	ng/dL	12.87	pmol/L
fT3	pg/mL	1.536	pmol/L
Calcitonin	pg/mL	0.293	pmol/L
Thyroglobulin	ng/mL	1.0	µg/L
Parathyroid and bone			
PTH	pg/mL	0.106	pmol/L
25-OH-D	ng/mL = µg/L	2.50	nmol/L
Adrenal			
Steroid hormones			
Cortisol	µg/dL	27.6	nmol/L
Aldosterone	ng/dL	27.7	pmol/L
17-OH-progesterone	ng/dL	0.0303	nmol/L
Androstenedione	ng/dL	0.0349	nmol/L
DHEA	ng/dL	0.0347	nmol/L
DHEAS	µg/dL	0.027	µmol/L
Catecholamines			
Plasma adrenaline (epinephrine)	pg/mL	0.00546	nmol/L
Plasma noradrenaline (norepinephrine)	pg/mL	0.00591	nmol/L

Urinary adrenaline (epinephrine)	µg/24 h	5.46	nmol/24 h
Urinary noradrenaline (norepinephrine)	µg/24 h	5.91	nmol/24 h
Urinary metanephrines	µg/24 h	5.07	nmol/24 h
Gonads			
Estradiol	pg/mL	3.67	pmol/L
Progesterone	ng/mL = µg/L	3.18	nmol/L
Testosterone	ng/dL	0.0347	nmol/L
Dihydrotestosterone	ng/dL	0.0344	nmol/L
Neuroendocrine			
Chromogranin A	ng/mL = µg/L	0.0208	nmol/L
Gastrin	pg/mL	0.476	pmol/L
Insulin	µIU/mL = mIU/L	6.9	pmol/L
C-peptide	ng/mL	0.331	nmol/L
Urinary 5-HIAA	mg/24 h	5.23	µmol/24 h

Conventional and SI units and conversion factors for some routine laboratory measurements

	Conventional units	Conversion factor to SI	SI units
Serum glucose	mg/dL	0.0555	mmol/L
Serum calcium	mg/dL	0.2495	mmol/L
Serum creatinine	mg/dL	88.4	µmol/L

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