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Section I

Clinical approaches

Chapter 1

Clinical presentations of endocrine diseases

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Endocrinology is a fascinating field that covers a wide range of diseases with an equally broad spectrum of clinical manifestations. While some endocrine diseases are suspected after the discovery of an incidental mass lesion, others may present as distinctive syndromes. Therefore, in addition to the unparalleled value of a good clinical history and physical examination, endocrinologists rely heavily on laboratory testing, imaging, and pathology. It is as important to the endocrinologist to know how to interpret ancillary testing as it is for the radiologist and pathologist to have a general understanding of the clinical correlates of imaging studies and tissue samples. The aim of this chapter is to provide the clinical presentations of selected endocrine diseases in the context of their pathological correlates

Pituitary adenomas

Clinical manifestations

The pituitary gland works in concert with the hypothalamus and peripheral endocrine glands by means of complex feedback loops. The result of this feedback mechanism is a well-coordinated cascade of events that leads to controlled pulsatile secretion of the anterior pituitary hormones: adrenocorticotropic hormone (ACTH), growth hormone (GH), prolactin, thyroid-stimulating hormone (TSH; also known as thyrotropin), follicle-stimulating hormone (FSH), and luteinizing hormone (LH). In addition to the tropic effect in their target organs, these hormones are essential for several functions, including metabolism, growth, and reproduction. Tumors that affect the pituitary gland may disturb these functions by a direct mechanical effect (compression of the normal pituitary tissue, impairment of blood flow, and interference with the hypothalamic–hypophyseal portal system) [1], or by excessive hormone production (Table 1.1). Moreover, due to the close proximity with the optic chiasm, large pituitary tumors may result in visual field defects [2,3] (Fig. 1.1). Invasive pituitary tumors may also cause cranial nerve palsies occurring in either the presence or the absence of pituitary apoplexy [4–6]; however, ophthalmoplegia should raise the suspicion of metastatic disease to the pituitary [7,8]. Rarely, giant pituitary tumors may also compress the temporal lobe resulting in complex partial seizures [9,10].

Pituitary tumors have an overall estimated prevalence of approximately 17% based on radiographical and autopsy studies [11]. Not all of these tumors will have deleterious clinical implications. Consequently, clinicians are faced with the following questions. Is the pituitary tumor functional or non-functional? Is there any evidence of compression of neighboring structures? Does the affected individual have a hereditary disease that predisposes to pituitary tumors? Is medical and/or surgical therapy warranted? Does this individual require follow-up and for how long?

Table 1.1. General clinical presentations of pituitary adenomas

Type of effect	Defects
Pituitary dysfunction	Hypersecretory syndromes Hyperprolactinemia Acromegaly Cushing disease Hyperthyroidism Hypopituitarism from hypersecretion of other pituitary hormones Hypogonadism from prolactin or glucocorticoid excess Growth hormone deficiency in the context of glucocorticoid excess
Mass effects	Headaches Hypopituitarism Visual field defects Blindness Visual acuity loss Optic atrophy Diplopia Ophthalmoplegia Trigeminal sensory loss Cavernous sinus syndrome Temporal lobe epilepsy

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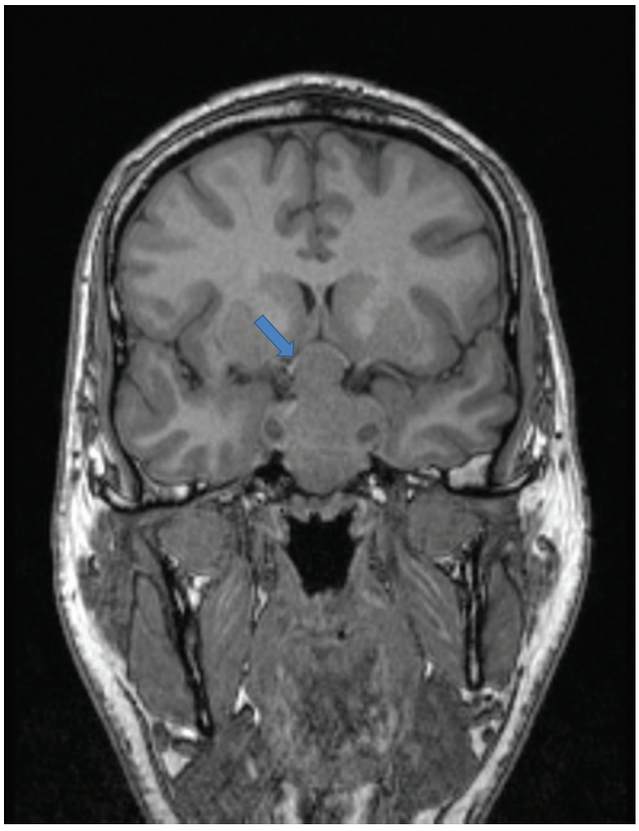

Fig. 1.1. Coronal T_1-weighted MPRAGE image of a large prolactinoma causing compression of the optic chiasm. This patient presented with bilateral temporal hemianopsia.

Hypopituitarism

Hypopituitarism is defined as the deficiency of one or more pituitary hormones. Biochemically, inappropriately normal or low levels of anterior pituitary hormones distinguish pituitary disorders from their primary counterparts.

There are multiple etiologies of hypopituitarism, including congenital, iatrogenic, inflammatory, and secondary to tumors affecting the pituitary. In hypopituitary patients with macroadenomas, somatotrophs, lactotrophs, and gonadotrophs are more frequently affected than thyrotrophs and corticotrophs [1]. This pattern contrasts with that of hypophysitis-related hypopituitarism, in which corticotroph cells are more commonly affected.

The clinical manifestations of hypopituitarism depend on the extent of hormone deficiencies and may be non-specific, such as malaise, fatigue, weight loss, reduced appetite, cold intolerance, and abdominal pain [1,12,13].

Hypogonadotropic hypogonadism

Women

Female hypogonadism refers to deficient or abnormal function of the hypothalamic–pituitary–ovarian axis resulting in estrogen deficiency and abnormal menstrual cycles [14]. Hypogonadotropic hypogonadism is a clinical syndrome that results from gonadal failure due to deficient pituitary gonadotropin secretion. Onset of the syndrome prior to menarche manifests as primary amenorrhea, absent or poor development of secondary sexual characteristics, and eunuchoid body habitus [15]. In adult women of reproductive age, hypogonadotropic hypogonadism presents as secondary amenorrhea (Fig. 1.2), infertility, decreased libido, dyspareunia, sleep disturbances, and osteoporosis [12,14,15]. In postmenopausal women, low or "normal" serum gonadotropins are diagnostic of secondary hypogonadism [12].

Men

Male hypogonadism is a clinical syndrome that results from testicular failure to produce physiological levels of testosterone and/or spermatozoa [16]. When it is due to disruption of pituitary function it is known as hypogonadotropic hypogonadism. Prepubertal onset of testosterone deficiency manifests as delayed puberty, absent or poor development of secondary sexual characteristics, and eunuchoid proportions. In adult men the symptoms and signs of testosterone deficiency include decreased libido, erectile dysfunction, reduced frequency of shaving, depression, fatigue, infertility, loss of drive, increased visceral fat mass, reduced muscle mass, and reduced testicular size [15,17–19]. Moreover, testosterone deficiency may result in anemia, and osteopenia and/or osteoporosis [18,20].

Hypogonadism should be investigated in men presenting with signs and symptoms of testosterone deficiency. In those individuals, confirmed low serum testosterone levels are diagnostic of hypogonadism (Fig. 1.3).

Growth hormone deficiency

In children GH deficiency manifests mainly as failure to grow and short stature [21]. In contrast, the syndrome of adult GH deficiency characteristically presents with a reduction in lean body mass, bone mineral density, muscle strength, exercise performance, and quality of life (fatigue, low mood and motivation, reduced satisfaction) [22–29]. Moreover, GH deficiency may result in systolic and diastolic cardiac dysfunction, premature atherosclerosis, increased ratio of total to high density lipoprotein cholesterol, and increased serum triglyceride levels [22–28].

Evaluation for adult GH deficiency should only be considered in individuals who are at high risk. These include patients with evidence of hypothalamic–pituitary disease, previous cranial radiation, or history of childhood GH deficiency [22] (Fig. 1.4). The gold standard for establishing the diagnosis of GH deficiency is the insulin tolerance test (ITT). However, the growth hormone-releasing hormone (GHRH)-arginine stimulation test is widely accepted as a potential alternative [30–32]. In situations where the ITT is contraindicated or the combined GHRH-arginine stimulation test is not available, the glucagon stimulation test may be considered [27].

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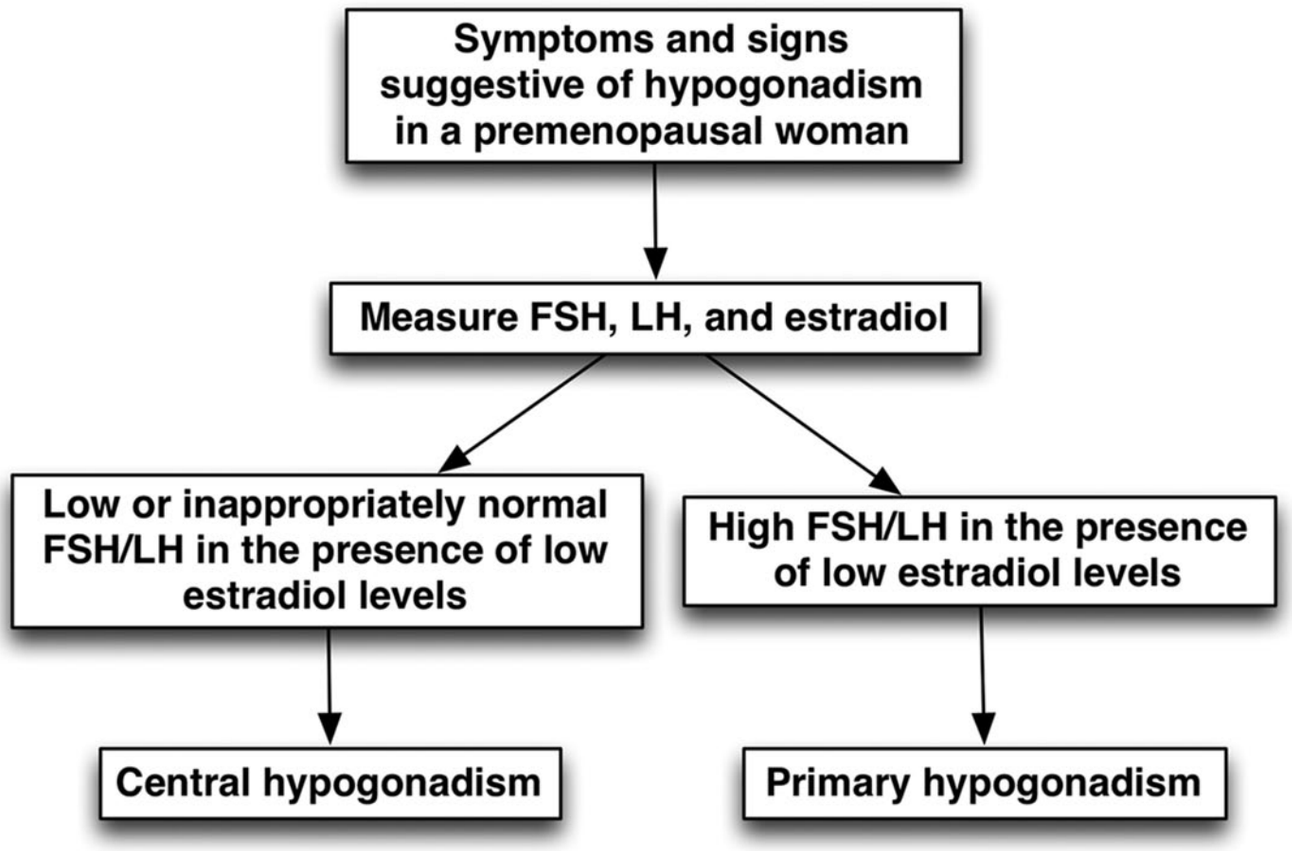

Fig. 1.2. Initial pituitary biochemical testing of premenopausal women with suspected hypogonadism. FSH, follicle-stimulating hormone; LH, luteinizing hormone.

Central hypothyroidism

Central hypothyroidism is defined as a defect of thyroid hormone production due to insufficient stimulation of the thyroid gland by the normal pituitary/hypothalamic drive [34]. In most cases, it is encountered in combination with other pituitary hormone deficits making it hard to distinguish symptoms from hypothyroidism alone [35]. Patients with central hypothyroidism tend to have milder symptoms than those with a primary defect and distinctively do not have a goiter [35]. The log/linear relationship between TSH and thyroid hormones dictates that individuals with primary hypothyroidism should have an elevated TSH [36,37]. Therefore, the biochemical hallmark of central hypothyroidism is the presence of a low or inappropriately normal TSH level in association with low free thyroxine [34,35,37].

Central adrenal insufficiency

Just as with central hypothyroidism, central adrenal insufficiency is generally accompanied by other pituitary hormone deficiencies. However, it can rarely be seen as an isolated event or as the first pituitary deficiency, such as in the context of lymphocytic hypophysitis [38]. Loss of ACTH drive for cortisol synthesis and secretion may be lethal and, therefore, it should be suspected, diagnosed, and appropriately treated.

The symptoms and signs of adrenal insufficiency may be acute in the form of an adrenal crisis (fluid-unresponsive severe hypotension) or gradual in onset, including weight loss, fatigue, nausea, vomiting, and weakness [39].

The ITT is considered the gold standard for the diagnosis of adrenal insufficiency as it tests the integrity of the entire hypothalamic–hypophyseal–adrenal axis. However, if central adrenal insufficiency is not believed to be an acute event, there are other alternatives such as the low- and high-dose corticotropin stimulation tests. Moreover, morning plasma cortisol levels can be very informative and in some selected instances obviate the need for dynamic testing (Fig. 1.5). A morning plasma cortisol level <100 nmol/L in an unstressed individual with possible central adrenal insufficiency generally correlates with a subnormal cortisol peak on an ITT that is diagnostic of adrenal insufficiency [40–42]. Provided that the patient is not stressed and/or has increased cortisol-binding globulin, a morning cortisol value >400 nmol/L generally excludes adrenal insufficiency [41].

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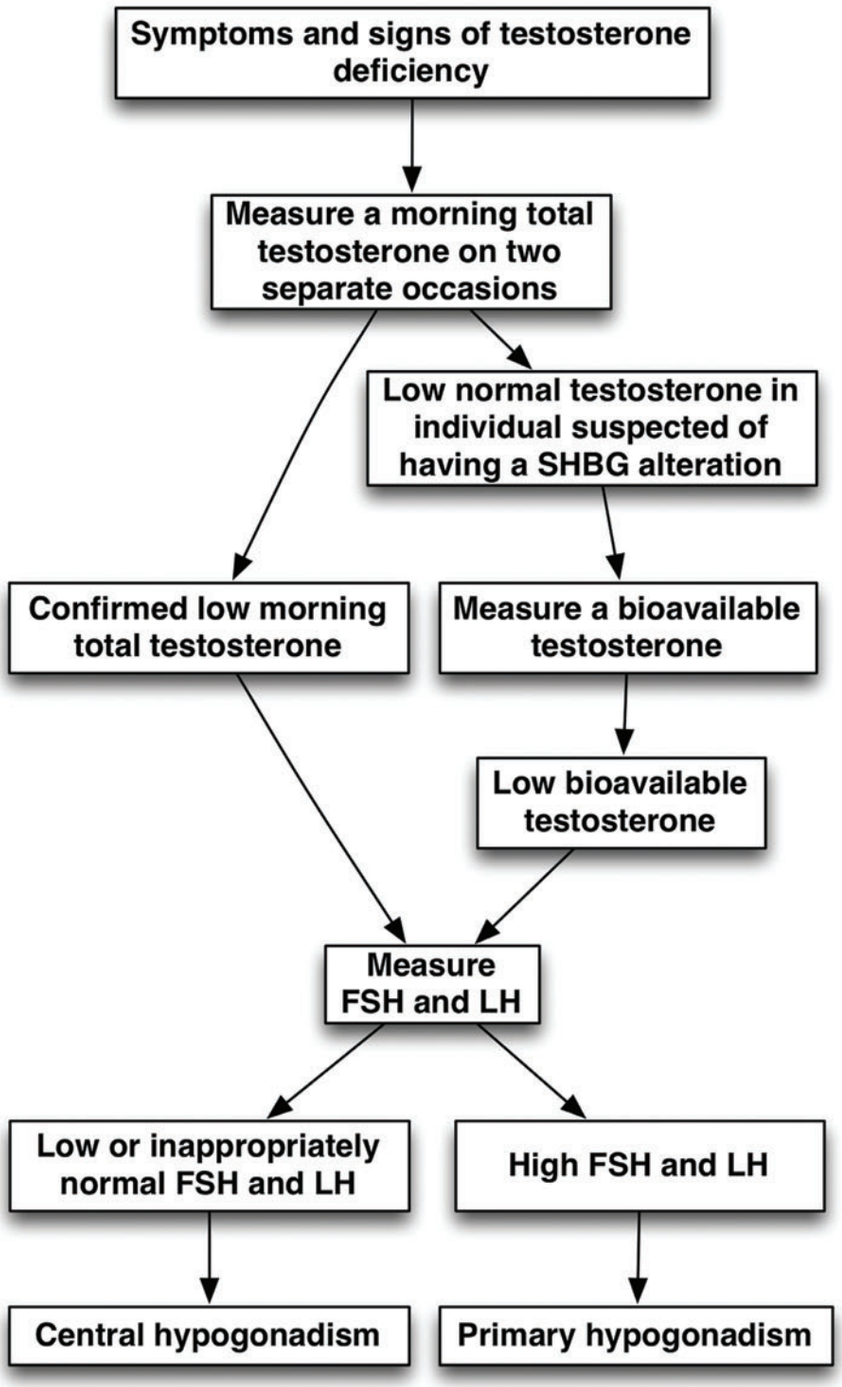

Fig. 1.3. Initial biochemical assessment of hypogonadism in adult men. FSH, follicle-stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone-binding globulin.

Furthermore, probably less than 4% of patients with a morning cortisol >350 nmol/L will fail the ITT [43].

Prolactin deficiency

Acquired prolactin deficiency in the absence of dopaminergic therapy has a low prevalence but when present it is suggestive of a more severe degree of anterior pituitary hypofunction [44,45]. Experience from the few reported cases of familial isolated prolactin deficiency indicates that prolactin is essential for normal lactation; hence puerperal alactogenesis would be the hallmark clinical manifestation of this deficiency [46–48].

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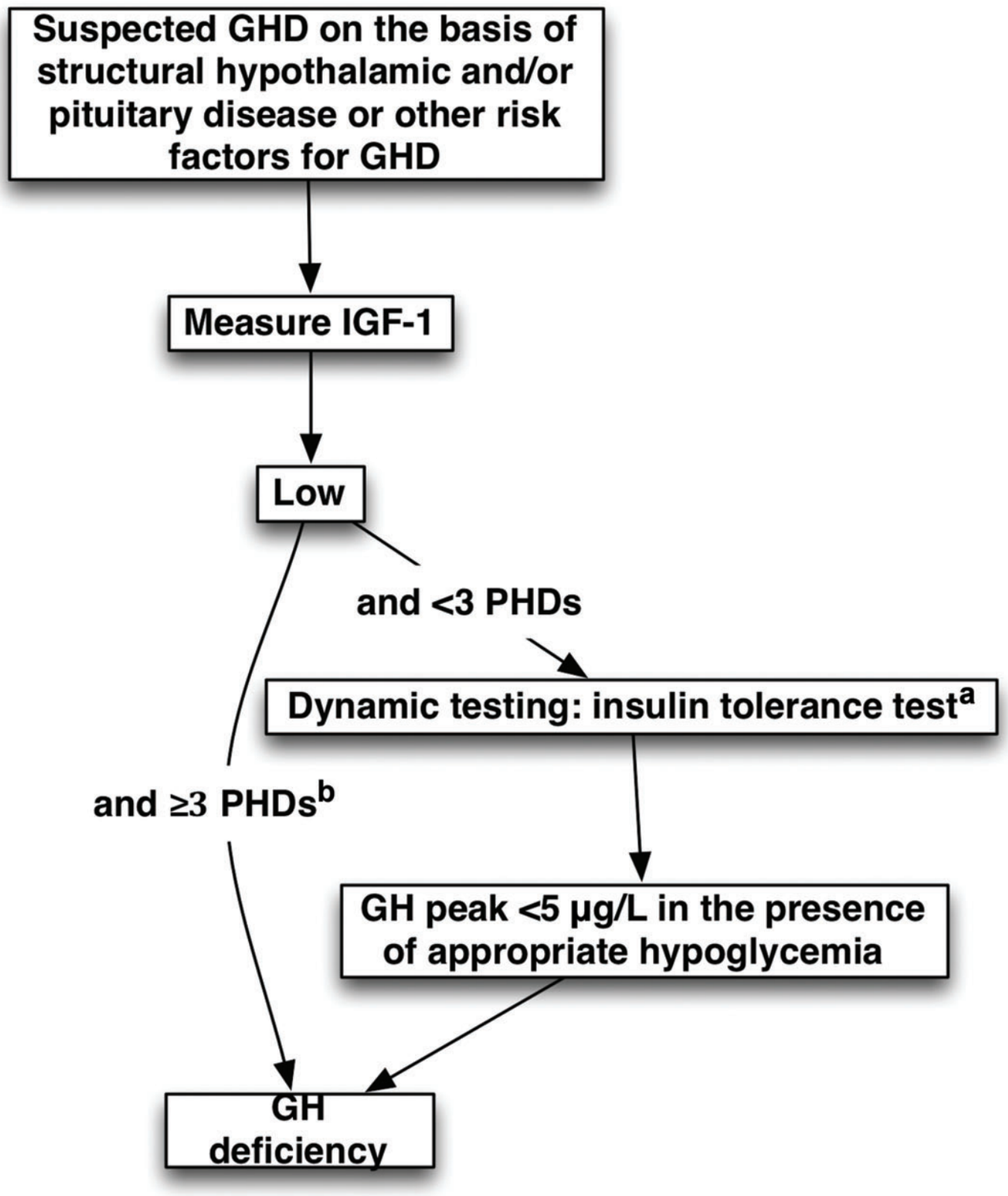

Fig. 1.4. Evaluation of adult growth hormone (GH) deficiency (GHD). [a]The growth hormone-releasing hormone (GHRH)-arginine test and glucagon stimulation are alternative tests; the cut-off values for GHD are different for these alternatives [30–32]. [b]A low level of insulin-like growth factor-1 (IGF-1) in the presence of three or more pituitary hormone deficiencies (PHDs) obviates the need for dynamic testing [33].

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Clinical classification of pituitary adenomas

Pituitary tumors that secrete excessive amounts of one or more hormones leading to a clinical syndrome are regarded as clinically functioning (Table 1.2). Tumors that lack those characteristics are classified as non-functioning pituitary adenomas (NFPA) or endocrinologically inactive. Gonadotroph tumors may secrete excessive amounts of gonadotropins, but in general, they are not associated with gonadal hormone excess or hypergonadism.

Another useful clinical classification of pituitary adenomas is based on tumor size. Pituitary adenomas that are <1 cm are termed microadenomas while tumors measuring ≥ 1 cm are referred to as macroadenomas [49].

Clinically non-functioning pituitary adenomas

Epidemiology

All adenoma subtypes can potentially present as clinically non-functioning. Nevertheless, based on surgical series, gonadotroph adenomas are by far the most frequent [50]. Most macroadenomas identified clinically are hormonally inactive or non-functioning.

Clinical presentation

Most patients with gonadotroph adenomas are middle-aged men [51,52]. The clinical manifestations of NFPA depend

Table 1.2. Clinical syndromes associated with anterior pituitary hyperfunction

Hormone secreted in excess	Clinical syndrome
Prolactin	Hypogonadism and galactorrhea
Growth hormone	Acromegaly, gigantism (before epiphyseal closure)
Adrenocorticotropic hormone	Cushing disease
Thyroid-stimulating hormone	Hyperthyroidism

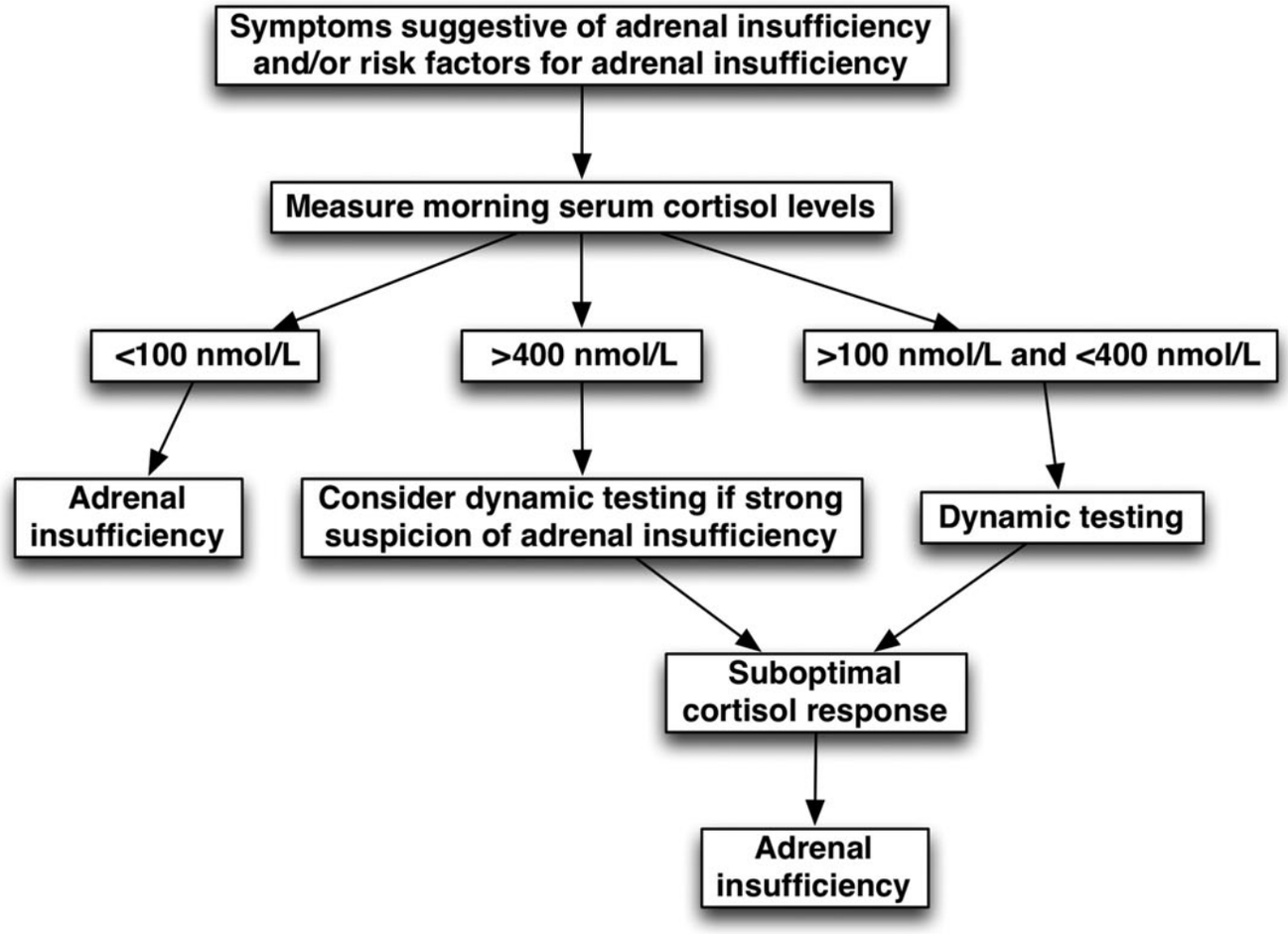

Fig. 1.5. Biochemical testing approach to the patient with suspected central adrenal insufficiency.

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mostly on tumor size. Microadenomas will often present as incidental finding on magnetic resonance imaging (MRI) whereas macroadenomas will more often manifest with hypopituitarism and/or compression of the optic chiasm. Visual symptoms are the most frequent presentation of non-functioning pituitary macroadenomas [52]. Nevertheless, once clinical investigations are undertaken, hypopituitarism is almost always present, with GH deficiency being the most frequent defect (85%), followed by hypogonadism (75%), adrenal insufficiency (38%), and hypothyroidism (32%) [53]. Hyperprolactinemia may also occur due to a stalk effect [54] but it is usually mild (<100–150 μg/L) [52, 55–57].

When compared with other NFPAs, silent corticotroph adenomas and silent subtype 3 adenomas seem to differ in some clinical characteristics. For example, silent corticotroph adenomas tend to be more frequently associated with the development of pituitary hemorrhage [58]. Silent subtype 3 adenomas are usually large and invasive. They are as frequent in women as they are in men but the mean age of presentation in women seems to be slightly younger (36.6 years) [57].

Clinical diagnosis

The clinical diagnosis of a NFPA is based on demonstrating the presence of a pituitary tumor with MRI or computed tomography (CT) with characteristics suggestive of an adenoma, together in some instances with inappropriately elevated gonadotropins or their subunits. Additionally, absence of biochemical evidence of other anterior pituitary hormone hypersecretion must be proven (with exception of mildly elevated prolactin levels, believed to be due to stalk effect). In men, FSH hypersecretion is a more common finding than abnormal elevations of LH [51,52], which partly explains why testosterone levels are rarely found to be elevated. Postmenopausal women have elevated gonadotropins, which hinders biochemical diagnosis. However, the typical scenario in the setting of a non-functioning pituitary macroadenoma is hypogonadism, reflected by an inappropriately low LH in more than 50% of patients and a low FSH in approximately 30% of patients [52]. An exaggerated gonadotropin response to TRH has also been previously used for the diagnosis of gonadotroph adenomas [59,60].

Management

Medical treatment is largely ineffective in the treatment of NFPA. Surgery is indicated for patients with tumors causing visual field deficits and it should also be considered in hypopituitarism [61] (Fig. 1.6).

Natural history and follow-up

Non-functioning pituitary microadenomas generally remain stable in size over time; approximately only 10% of them grow during the initial years of follow-up [62]. In contrast,

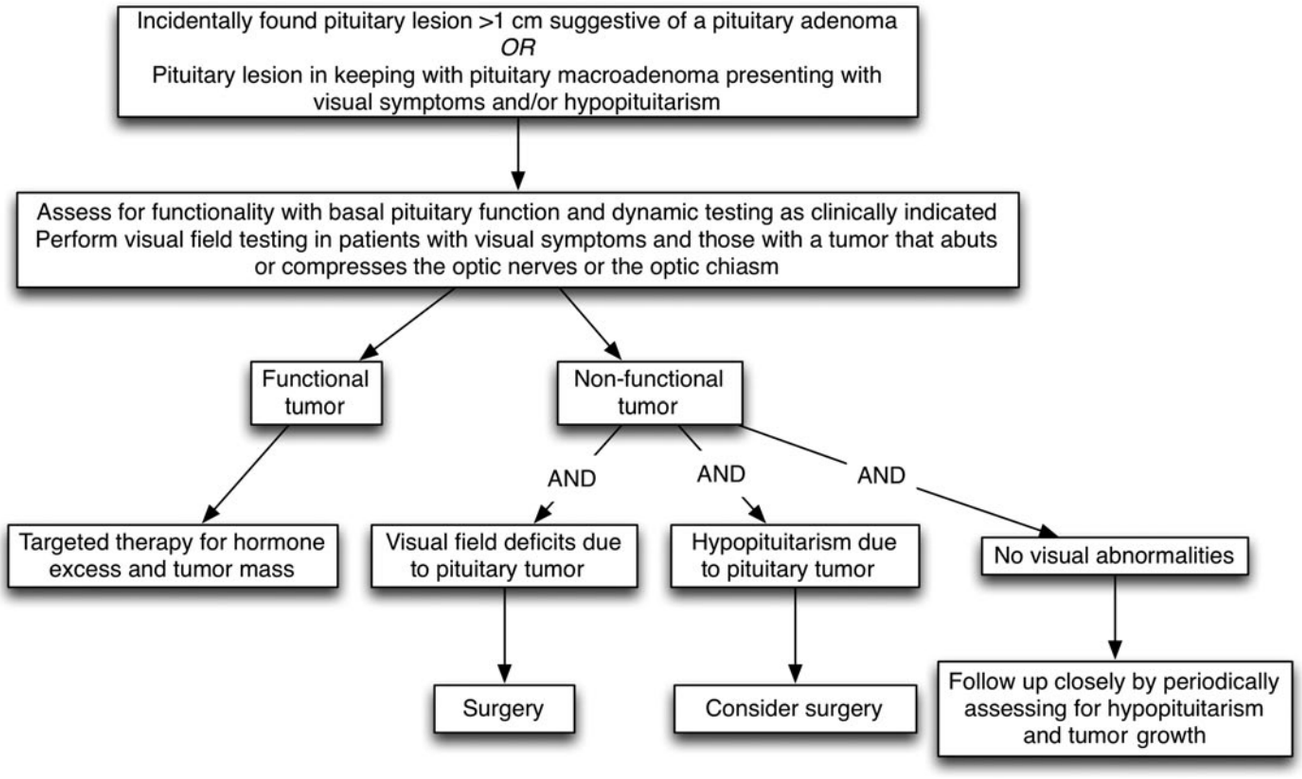

Fig. 1.6. Approach to pituitary lesions >1 cm suggestive of pituitary macroadenomas.

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up to 50% of macroadenomas that have been followed for approximately 5 years show an increase in size [53]. Additionally, after surgery alone, nearly 30% of patients relapse within 5 to 10 years [63]. Furthermore, even though the overall recurrence of silent corticotroph adenomas seems to be similar to that of other NFPA [58,64], young patients with silent corticotroph adenomas may have a higher frequency of multiple and late recurrences [64]. All of this information must be taken into account when designing an appropriate follow-up; however, as a general rule, all NFPA that are >1 cm should be followed long term with imaging and testing of pituitary function whereas a more conservative approach is adequate for small lesions that have demonstrated stability in size.

Prolactinoma

Epidemiology

Prolactinomas are the most frequently encountered functioning pituitary tumors and occur more commonly in women of reproductive age [65]. Most prolactinomas are sporadic; nevertheless, prolactinomas are a frequent manifestation of multiple endocrine neoplasia type 1 (MEN1).

Clinical presentation

Hyperprolactinemia causes suppression of the hypothalamic–pituitary–gonadal axis [66]; therefore, its clinical hallmark is hypogonadism. The clinical presentation of prolactinomas varies with tumor size and gender.

Women

In women of reproductive age, the typical clinical presentation is that of a microprolactinoma associated with galactorrhea and/or amenorrhea [67]. Other manifestations of hypogonadism such as infertility and low bone mineral density, predominantly of trabecular bone, may also be present [68–70]. Postmenopausal women with tumoral hyperprolactinemia typically present with large adenomas and symptoms of mass effects such as headaches and visual field defects [70].

Men

In contrast to women, men present more frequently with macroprolactinomas and more invasive disease [67,71]. In this setting, it is not surprising that men typically present with decreased libido, visual field defects [67,72], and some degree of hypopituitarism, with loss of LH and FSH followed by GH, TSH, and ACTH [73]. Gynecomastia and galactorrhea are much less frequent [67,72,73]. Men with prolactinomas have a lower bone mineral density and are at higher risk of vertebral fractures than controls [74].

Diagnosis

The secretion of prolactin is regulated mainly by dopamine inhibition and hence disruption of the pituitary stalk and drugs that inhibit dopamine secretion may cause hyperprolactinemia. Additionally, pregnancy and lactation constitute states in which the elevation of prolactin is physiological. In order to appropriately interpret prolactin levels and to reach the clinical diagnosis of a prolactinoma, a critical understanding of the various conditions in which prolactin may be elevated as well as the expected degree of elevation is required. Moreover, it is important to recognize that true prolactinomas exhibit a size correlation with the degree of prolactin elevation [67,75].

The clinical diagnosis of a prolactinoma is based on elevated levels of plasma prolactin in association with a pituitary tumor and no evidence of another cause of hyperprolactinemia (Fig. 1.7). Medication-induced hyperprolactinemia is usually mild (<150 μg/L) [76]. When a medication is believed to be the cause of hyperprolactinemia, it should be discontinued (when possible) for 3–4 days and the prolactin level reassessed [77]. Prolactin levels >150 μg/L, are rarely due to a stalk effect caused by a NFPA [52,55–57]. However, such mildly elevated levels may also be seen in the context of large prolactinomas due to the "hook effect" [78,79]. Therefore, if a hook effect is suspected, prolactin should be diluted and remeasured. Most patients with plasma prolactin >150–200 μg/L will have a prolactinoma [70,80] and macroprolactinomas are usually associated with prolactin levels >250 μg/L [70].

Acromegaly

In 1886, the French physician Pierre Marie used the term acromegaly to describe a condition in which there was enlargement of the face, hands, and feet [81]. During the following years it became clear that gigantism was a form of the same disease occurring when the skeleton harbored the potential to grow. At the end of the nineteenth century and beginning of the twentieth, the relationship between pituitary tumors and acromegaly was established. Of special relevance was Harvey Cushing's report in 1909 of the remission of symptoms of acromegaly after performing a partial hypophysectomy on a patient who had been referred to him by Dr. Charles H. Mayo [82]. Years later the physiopathological roles of GH and insulin-like growth factor-1 (IGF-1) were characterized and with that advance came the recent definition of both disorders. Gigantism is a condition of GH excess that occurs before epiphyseal fusion and hence is phenotypically characterized by tall stature, whereas acromegaly occurs after epiphyseal closure and is characterized by acral growth. Both conditions are progressive if not treated and may be associated with several systemic manifestations that include organ enlargement and metabolic complications.

Epidemiology

The prevalence of acromegaly is 40 to 60 cases per million and the incidence is 2.1 to 4 cases per million per year [83,84]. It is usually diagnosed in the fourth decade of life and it is as frequent in men as it is in women [85].

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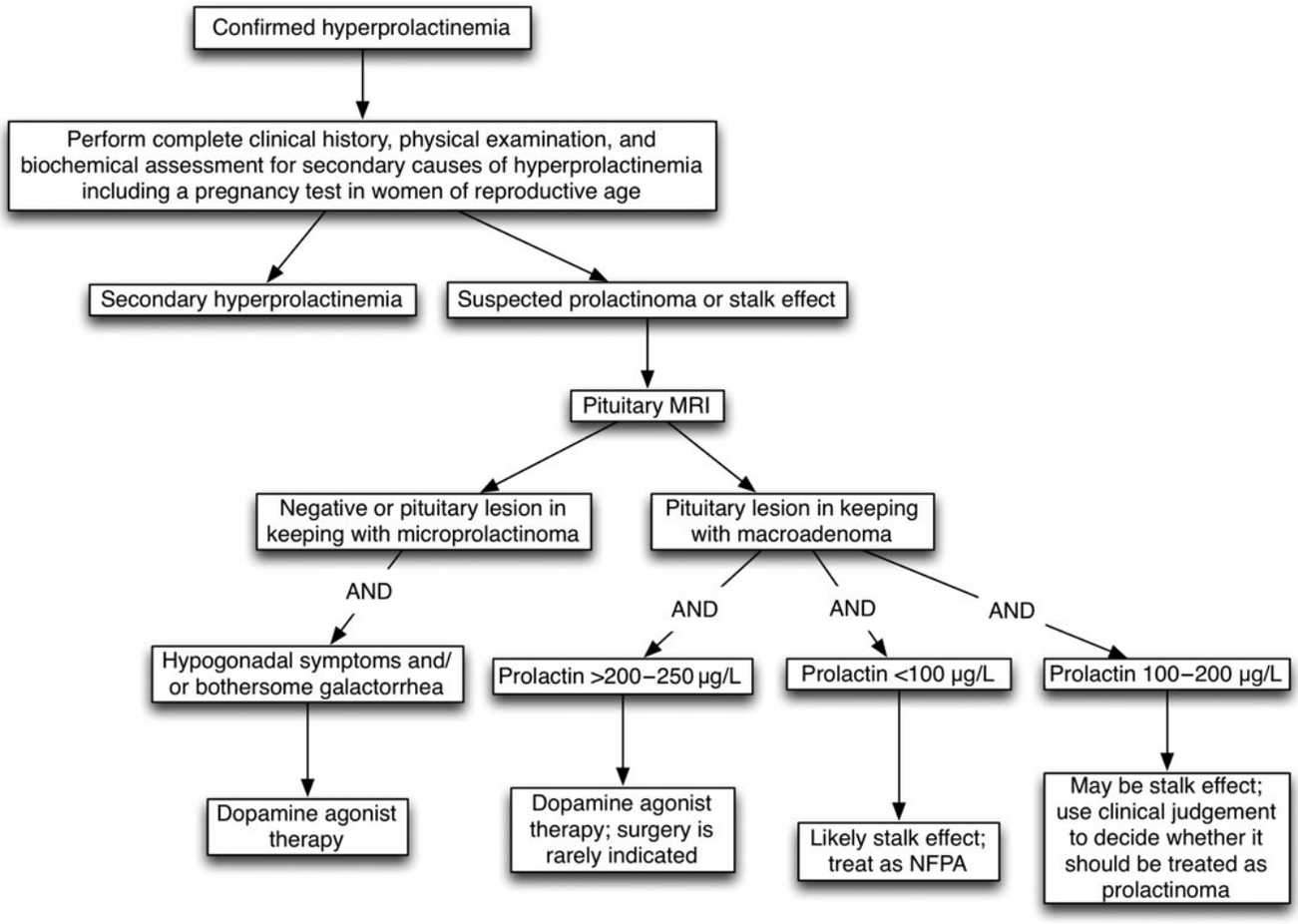

Fig. 1.7. Algorithm for the assessment and treatment of hyperprolactinemia of suspected tumor or pituitary stalk effect origin. NFPA, non-functioning pituitary adenoma.

Etiology and genetics

Acromegaly and gigantism may be sporadic or hereditary. Sporadic disease has been associated with a number of somatic gene mutations including *GNAS* mutations, which are found in up to 40% of GH-producing adenomas [86]. Contrary to the prognostic implications that morphology confers, the identification of *GNAS* mutations does not seem to aid in predicting response to therapy. Familial acromegaly/gigantism is due to germline mutations in the following genes: *AIP* (encoding aryl hydrocarbon receptor interacting protein) [87], *MEN1*, and *PRKAR1A* (encoding regulatory subunit type 1A of cyclic adenosine 5′-monophosphate-dependent protein kinase) [88]. Because of the high frequency of *MEN1* and *AIP* mutations in younger individuals (<21 years with pituitary adenomas of any size, or ≤30 years with macroadenomas) presenting with acromegaly/gigantism, genetic testing should be considered [89,90]. More recently an individual with an *SDHD* mutation and multiple paragangliomas was found to have acromegaly but more studies are needed to clearly establish whether *SDHx* mutations predispose to pituitary tumors [91].

Acromegaly is caused by pituitary or extrapituitary tumors that secrete GHRH or GH. Pituitary acromegaly is a consequence of a variety of neoplastic/hyperplastic lesions; however, somatotroph macroadenomas are by far the most common [92] (Table 1.3). Somatotroph adenomas may be densely granulated or sparsely granulated; this difference is relevant in that response to medical therapies varies amongst those two groups.

Clinical manifestations

Acromegaly is a slowly progressive condition. The development of symptoms is insidious and for that reason the diagnosis is typically delayed for approximately 8 years [84]. There is a wide range of clinical manifestations (Table 1.4) but more than 90% of patients with acromegaly present with acral growth, coarsened facial features, and soft tissue swelling (Fig. 1.8) [85]. It is still controversial whether acromegalic

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Table 1.3. Clinicopathological correlations in acromegaly/gigantism

Neoplastic/ hyperplastic lesions that cause acromegaly or gigantism	Relevant clinical correlations
Densely granulated somatotroph adenoma	Most common subtype of somatotroph adenoma [93] Responds better to somatostatin analogs than sparsely granulated adenoma [94] More frequently associated with glucose abnormalities than mixed tumors [92]
Sparsely granulated somatotroph adenoma	Larger, more invasive, and occurring in younger patients than densely granulated somatotroph adenoma [93] More frequently associated with glucose abnormalities than mixed tumors [92]
Mammosomatotroph adenoma and mammosomatotroph hyperplasia	In contrast to somatotroph adenoma, there is secretion of prolactin in addition to GH [95] Some patients with Carney complex may have mammosomatotroph adenomas and/or hyperplasia [96–98] Patients with McCune–Albright syndrome have been shown to have mammosomatotroph adenomas and hyperplasia [99, 100]
Somatotroph hyperplasia	Most commonly occurs as consequence of ectopic GHRH secretion from foregut neuroendocrine tumors, usually pancreatic or bronchial [101,102]; in patients with pancreatic GHRH secretion causing acromegaly, multiple endocrine neoplasia type 1 is a common finding [102] May be found in patients with McCune–Albright syndrome [100]
Acidophil stem cell adenoma	May secrete both GH and prolactin, but prolactin secretion predominates [103,104] Aggressive clinical behavior [105] Clinical signs of acromegaly may be observed without a marked elevation of random GH ("fugitive acromegaly") [105,106]
Gangliocytoma	This is an extremely rare cause of acromegaly. Gangliocytomas may be indistinguishable clinically and radiologically from somatotroph adenomas [107] and may be found in conjunction with a somatotroph adenoma or alone [108]

GH, growth hormone; GHRH, growth hormone-releasing hormone.

Table 1.4. Clinical manifestations of acromegaly

Area affected	Manifestations
Skin, bones, joints, and muscles	Acral growth, thickened skin, hyperhydrosis Osteopenia or osteoporosis, osteoarthritis Carpal tunnel syndrome Proximal myopathy
Thyroid	Nodular goiter
Cardiovascular	Hypertension, biventricular hypertrophy, arrhythmias
Respiratory	Macroglossia, sleep apnea, sinusitis
Liver	Low sex hormone-binding globulin
Gonadal function	Menstrual irregularities, sexual dysfunction
Colon	Colon polyps
Metabolic and other endocrine	Impaired glucose tolerance, diabetes, increased levels of calcitriol, which may lead to hypercalcemia, hypercalciuria, and hyperphosphatemia
Others	Decreased energy, depression

The information contained in this table was obtained from publications addressing the clinical features of acromegaly [85, 115–119].

individuals harbor a higher risk for overall cancer [109]. Data suggest that the specific types of tumor that may be more frequent in these individuals include differentiated thyroid cancer [110–112] and colon polyps [110,113,114].

The vast majority of patients with acromegaly have sporadic disease. Familial forms of gigantism/acromegaly should always be suspected in the pediatric population and when there is a family history of pituitary adenomas, MEN (1 or 4), or Carney complex.

Diagnosis

Elevated random GH levels are generally not sufficient to establish the diagnosis of acromegaly. For example, malnutrition, chronic kidney or hepatic disease, and oral estrogens can result in high levels of GH due to relatively low IGF-1 levels [120]. Contrary to GH, IGF-1 levels are rarely elevated in conditions other than acromegaly with the exception of pregnancy and adolescence. For those reasons the diagnosis of acromegaly is based on proving a non-suppressible (autonomous) GH secretion that is accompanied by an elevated IGF-1 [121]. This is done by means of an oral glucose tolerance test (OGTT) with 75 g of glucose. Normal individuals are expected to have a GH nadir $<0.4\,\mu g/L$ during the OGTT [122]. When the diagnosis of acromegaly has been made and adequate pituitary imaging is negative for

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