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5.1 Introduction

Acromegaly is a typical rare multisystemic disease associated with progressive enlargement of some parts of the body, featuring somatic disfigurement mainly involving the face and extremities. The archetypal body changes and gigantism are renowned features (Figs. 5.1 and 5.2). Apart from body changes and disproportion, a number of multiorgan comorbidities are frequently associated with acromegaly. Most clinical repercussions originate from growth hormone (GH) and insulin-like growth factor-1 (IGF-I)-dependent organ overgrowth. In most cases, GH excess is due to a pituitary adenoma. Acromegaly itself and the related comorbidities might lead to premature death if not adequately treated.

5.2 Epidemiology

The prevalence of acromegaly has recently been estimated to be approximately 28 to 137 cases per million inhabitants [3, 4], challenging the historical figure of 40 to 70 cases per million [5]. A prevalence of approximately 1000 per million inhabitants was found in a German study based on screening with IGF-I measurement in

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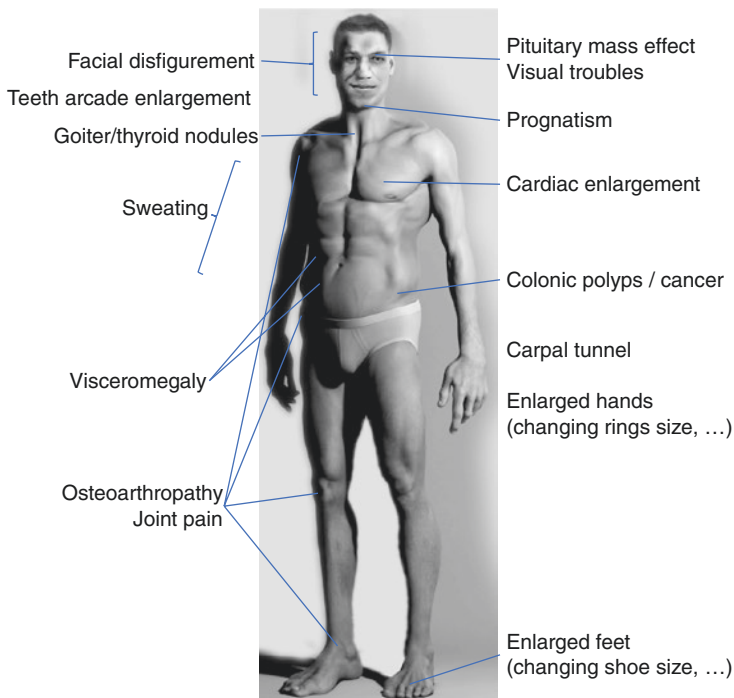


Fig. 5.1 Schematic representation of signs and symptoms of acromegaly. Adapted from [1], with permission



Fig. 5.2 Disease evolution in a woman with acromegaly. Series of photographs taken over time showing the progressive changes in facial appearance. It is possible to presume that the first signs appeared between 1988 and 1990, 22 years before the diagnosis. In 1990, the patient had to enlarge her ring she bought 2 years before because it was too narrow (adapted from [2], with permission)

the general population [6]. Raappana estimated the annual incidence of acromegaly at 3.4 cases per million in Finland [7]. A recent survey analyzing all the studies providing epidemiological data refined the incidence to a range between 0.2 and 1.1 cases/100,000 [8].

Age at diagnosis typically falls within the fourth decade of life, following a quasi-Gaussian curve [9, 10]. However, although more rarely, acromegaly might be found in children and in the elderly.

The sex ratio has been found to be more or less constant across studies. A female to male ratio of 1.26 has been calculated by analyzing data concerning more than 16,000 patients across national registries [11]. Age at diagnosis is typically earlier in males than in females, and a clearly distinguishable sex-related dimorphic Gaussian curve is observed [9, 12, 13].

Owing to the insidious clinical onset and slow progression, acromegaly is often diagnosed late. Older series, in the 1980s, suggested a mean diagnostic latency of 3–10 years after onset, at an average age of approximately 40 years [8, 14–17].

Studies focusing on disease latency seem to show that diagnostic delay appears to be more or less constant throughout decades, without any improvement over time with an earlier diagnosis [9, 18].

5.3 Pathogenesis

In more than 95% of cases, acromegaly is secondary to GH hypersecretion by a benign monoclonal pituitary adenoma that develops from somatotroph cells [19–22]. Pituitary somatotroph adenomas are mostly isolated (sporadic). Rarely, they may develop in the frame of a genetic predisposing disease (Fig. 5.3a).

5.3.1 Somatotroph Pituitary Adenoma

Pure somatotroph pituitary adenomas (60%) are constituted by eosinophilic cells containing either densely or sparsely granulated (secretory granules) cell elements after immunolabeling [19]. In some adenomas, immunostaining reveals colocalization of free alpha-subunits [24]. Silent somatotroph adenomas do not determine clinical acromegaly. Diagnosis is almost exclusively made by tumor immunostaining. Nonetheless, some patients bearing these tumors may have supranormal circulating GH levels without overt clinical signs [25].

Most human somatotroph adenomas seem to be associated with the clonal expansion [26] of cells carrying a specific somatic mutation. However, as in other types of pituitary adenoma, it has proven difficult to isolate a single causative factor explaining pituitary tumorigenesis [27–29]. Mutations in stimulating G-protein [30, 295] have been identified in 35–55% of somatotroph adenomas, according to some series [30–32]. *gsp* mutations are able to inhibit GTPase activity and to lead to constitutive adenylyl-cyclase activation [33]. Cell cycle disruption also seems to play an important role, as demonstrated in MEN1 or in patients with *CDKN1B* mutations (coding the

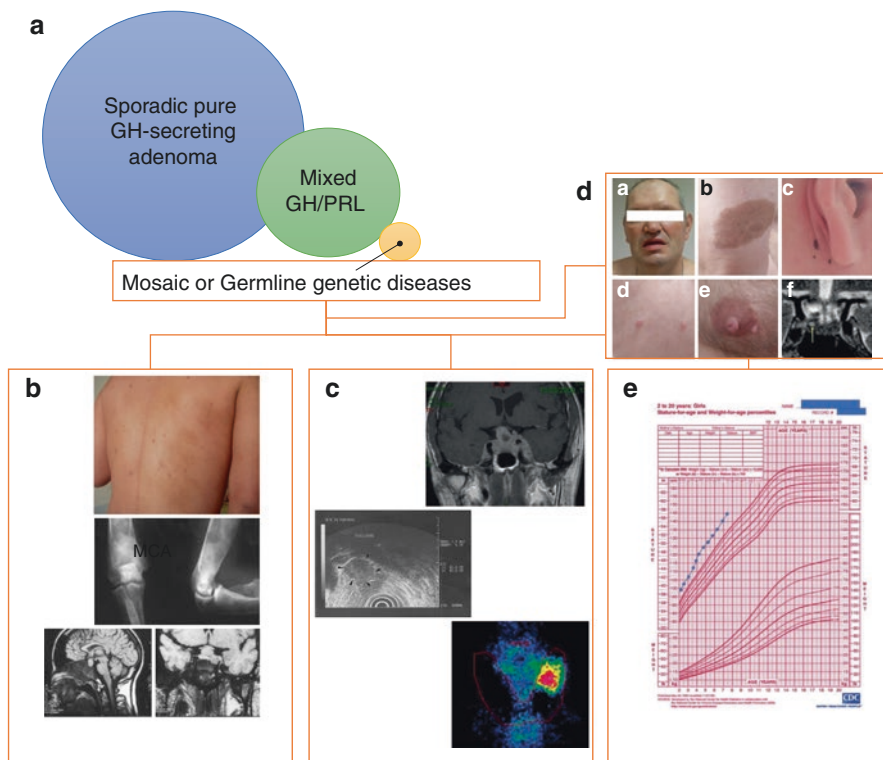


Fig. 5.3 Prevalence of somatotroph tumor forms and associated clinical genetic diseases. Panel a: Schematic representing the relative prevalence of sporadic pure or mixed somatotroph adenomas and associated mosaic/germline genetic diseases. Panel b: Characteristic clinical features of a patient with McCune Albright syndrome. Please note the typical café-au lait skin spots and X-rays and MRI hallmarks illustrating fibrous bone dysplasia. Panel c: Characteristic clinical features in a patient with acromegaly with multiple endocrine neoplasia type-1. Please note the pituitary tumor on a MRI T1W coronal post-gadolinium view, a pancreatic tumor revealed by echoendoscopy, and parathyroid hyperplasia/adenoma found on ^{99m}Tc - ^{123}I subtraction parathyroid scintigraphy. Panel d: Characteristics of a patient with Carney complex, from [23], with permission. Panel e: Growth curve of a patient affected by X-LAG acro-gigantism

cyclin-dependent kinase inhibitor p27KIP1, a key regulator of the cell cycle) [29]. A number of other genes have been implicated in somatotroph tumorigenesis [29]. The function of the disrupted proteins deriving from mutated genes spans from oncogene/tumor suppression to cyclin/cell proliferation inhibition. The general belief is that a preexisting mutation within somatotrophs should be a predisposing factor for further cell proliferation and GH secretion. Premature senescence likely explains the persistence of a benign phenotype and the rarity of progression to carcinoma. Epigenetic mechanisms may also contribute to cell proliferation by silencing genes such as *CDKN2A*, encoding p16, a cell proliferation inhibitor. The sequence of events leading to somatotroph cell clonal expansion seems to be multifactorial [34, 35].

Cytogenetic studies show that somatotroph pituitary adenomas display substantial intertumor and intratumor DNA copy-number heterogeneity. Intriguingly, somatic *GNAS*-mutated adenomas have low copy number variations, whereas a higher heterogeneity is observed in *GNAS*-intact tumors [36].

5.3.2 Mixed Somatotroph Adenoma

The most frequent mixed adenomas coexpress GH and prolactin (PRL), accounting for 25% of cases. Histopathologists often distinguish between true mixed adenomas, containing either somatotroph or lactotroph cell types, and lactosomatotroph stem cells consisting of more mature monomorphic cells coexpressing GH and PRL [19]. Mixed GH- and TSH-secreting adenomas are rarer and are associated with acromegaly associated with hyperthyroidism by inappropriate secretion of thyroid-stimulating hormone [37, 38]. ACTH cosecretion in somatotroph adenomas is extremely rare.

5.3.3 Genetic Syndromes Associated with Acromegaly

Various genetic syndromes and diseases include acromegaly in a wider spectrum of clinical features. Despite representing a rare cause, the burden of related morbidities requires not neglecting them (Fig. 5.3a–e). This paragraph summarizes the main features of these diseases along with some peculiarities in acromegaly manifestation. In general terms, a germinal genetic disorder should be suspected in patients with early-onset acromegaly bearing other organ involvement. These diseases have also been reviewed in recent articles and book chapters [20, 39–42].

McCune-Albright syndrome (MAS) is a rare genetic disease associated with multiple fibrous bone dysplastic lesions, precocious puberty, “café-au-lait” spots, and multiorgan and soft-tissue tumors (Fig. 5.3b). Pathological features are related to postzygotic somatic mutations leading to constitutive activation of the Gs protein alpha subunit [43–45]. It is of note that this gene is also responsible for most sporadic pure GH adenomas, underlying the importance of stimulating G-protein in the somatotroph environment. In the case of diffuse germinal mutations (MAS), acromegaly is found in approximately 20% of patients [43, 44, 46]. A peculiarity of this form is a relative resistance to somatostatin analogs (approximately 30% of responders). The therapeutic approach is also markedly influenced by the coexistence of skull base dysplasia, making any neurosurgical approach challenging [45].

Acromegaly can also be associated with hyperparathyroidism, neuroendocrine tumors (e.g., gastrinoma, insulinoma, or a nonfunctional pancreatic tumor), adrenal and other endocrine or nonendocrine tumors in the frame of **multiple endocrine neoplasia (MEN) type 1**, which is related to *menin (MEN1)* germline mutations (Fig. 5.3c) [47, 48]. Pituitary adenomas are not enriched in the somatotroph lineage in MEN1 patients. Few cases of GHRH-secreting neuroendocrine tumors have been reported in patients with MEN1 (see the “Extrapituitary acromegaly” paragraph) [49, 50].

Mutations in the *CDKN1B* gene are responsible for a rarer and newer MEN syndrome, **multiple endocrine neoplasia type 4** (MEN4, initially known as MEN-X), which combines hyperparathyroidism, pituitary adenomas (including acromegaly), and other endocrine or nonendocrine tumors [51, 52]. Twenty cases have been published to date. Hyperparathyroidism seems to be the most prevalent disease. Nonetheless, acromegaly by a somatotroph adenoma is found in up to 20% of patients harboring a deleterious *CDKN1B* mutation. Furthermore, contrary to MEN1, pituitary adenomas in MEN4 seem to be more enriched in somatotroph adenomas.

When acromegaly is associated with bilateral pigmented micronodular adrenal hyperplasia (causing ACTH-independent hypercortisolism) or with typical cutaneous pigmentations or cardiac myxomas, the patient should be screened for the **Carney complex** (Fig. 5.3D). This genetic disease is related to a germline mutation of the regulatory subunit of protein kinase A (*PRKARIA*), whose signaling cascade is also located downstream of the stimulating G-protein [53, 54]. A simplified schematic of the cyclic AMP-dependent signaling pathway with relevant targets for somatotroph tumorigenesis is provided in Fig. 5.4.

Acromegaly is also one of the features described in **familial isolated pituitary adenoma**, partly related to *AIP* germline mutations (aryl hydrocarbon receptor interacting protein) [55–57]. These mutations can also, albeit rarely, be found in some apparently sporadic cases of acromegaly, particularly in young patients [58–62].

GPR101 was the latest gene to be discovered in association with a very early-onset form of **X-linked gigantism** or **X-LAG syndrome** [63]. Affected patients develop large or giant adenomas at a very young age. The pathophysiology is related to Xq26.3 microduplication involving the orphan G-protein-coupled receptor GPR101. However, germline GPR101 mutations are very rare in patients with sporadic pituitary adenomas, particularly in patients with gigantism or acromegaly [64]. Little is known about the pathophysiology and sequence of events leading to somatotroph tumorigenesis (Fig. 5.3E).

5.3.4 GH-Secreting Carcinomas

Somatotroph carcinomas are exceptional (fewer than 20 published cases). The presence of distant metastases is required to support the diagnosis of malignancy [39].

5.3.5 Extrapituitary Acromegaly

Extrapituitary acromegaly refers to growth hormone releasing hormone (GHRH) or GH hypersecretion other than from a pituitary adenoma [39].

GHRH hypersecretion could originate either from hypothalamic tumors, such as gangliocytomas, hamartomas, choristomas, and gliomas, or from the periphery. More often, GHRH hypersecretion comes from ectopic sources. The GHRH peptide

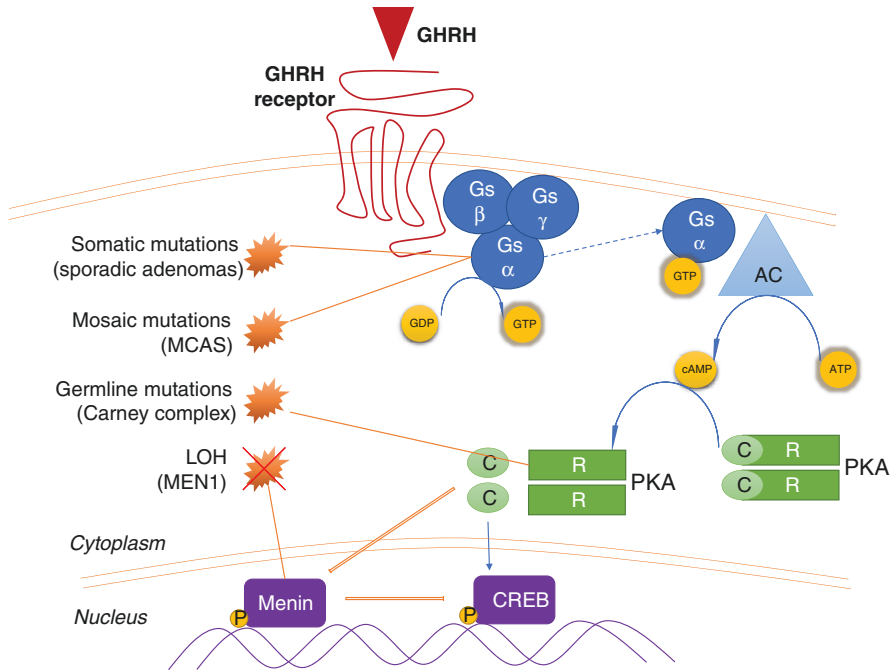


Fig. 5.4 The cyclic AMP-dependent signaling pathway in pituitary somatotroph cells as a model to understand different disease forms. GHRH induces a conformational change in the class II G protein-coupled receptor GHRHR. The Gs- α subunit exchanges GDP for GTP, which activates adenylyl cyclase (AC), converting ATP to cAMP. Elevated cAMP levels activate protein kinase A (PKA). PKA consists of a tetramer of two homo- or heterodimer regulatory subunits (R) and two catalytic subunits (C) responsible for the phosphorylation of several enzymes and transcription factors downstream [e.g., cAMP-response element-binding protein (CREB)]. *MCAS* McCune-Albright syndrome, *LOH* loss of heterozygosity, *MEN1* multiple endocrine neoplasia type-1, α , β , γ Gs-protein subunits, *AC* adenylyl cyclase, *cAMP* cyclic AMP, *CREB* cyclic AMP response element-binding protein, a transcription factor, *PKA* protein kinase A, *R* the regulatory subunits of protein kinase A, *C* the catalytic subunit of protein kinase A

was indeed originally identified and cloned from large pancreatic tumors [65]. GHRH is expressed by several tissues. However, very large amounts are needed to induce pituitary somatotroph hyperplasia and clinical acromegaly. GHRH hypersecretion may derive from pancreatic cell tumors, small-cell lung cancers, bronchial and other-site carcinoids, adrenal adenomas, and pheochromocytomas. The delivery of high GHRH concentrations stimulates normal pituitary somatotrophs to become hyperplastic and to hypersecrete GH to produce acromegaly [50, 66, 67]. The diagnosis is established by measuring plasma GHRH and by identifying the source (a GHRH-staining neuroendocrine tumor) [68]. The prognosis largely depends on the characteristics of the underlying tumor [50].

GH can also be directly secreted by an ectopic somatotroph adenoma (located near the *sella turcica*, for example, in the sphenoidal sinus, petrous temporal bone,

nasopharyngeal cavity) or, in exceptional cases, by a peripheral tumor (pancreatic islet tumor or lymphoma) [69, 70].

5.4 Clinical Presentation

Acromegaly is generally suspected based on clinical signs and symptoms, which are important to recognize (Fig. 5.1) [2, 16, 17, 71–74].

5.4.1 The Dysmorphic Syndrome

In typical forms, patients present broadened extremities (hands and feet), widened, thickened and stubby fingers, and soft tissue thickening. When specifically asked, affected patients describe enlarged rings over the last years or the need to change shoe size. The facial aspect is somehow characteristic and includes a widened and thickened nose, prominent cheekbones, bulged forehead, thick lips, and marked facial lines (Figs. 5.1 and 5.2). The forehead and the overlying skin are thickened, sometimes leading to frontal bossing. The lower face is also affected, with several degrees of prognathism, maxillary widening, teeth separation, and, more rarely, jaw occlusion impairment. A useful step is to analyze comparatively ancient photographs. This could show a slow, insidious demarcation of the acrofacial syndrome spreading over several years (Fig. 5.2). Because of this slow progression, relatives and physicians may be unaware, and acromegaly may be diagnosed very late. Typically, after variable latency, the diagnosis is raised by a physician who has not seen the patient before [16, 17, 75]. A recent multicenter survey investigating medical practices of more than 3000 patients with acromegaly across several European countries reported that most diagnoses were reportedly made by an endocrinologist (45%), followed by general practitioner (17.5%), internist (13.2%), orthopedist (3.6%), neurologist (3.3%), ophthalmologist (2.3%), and the patient him or herself or one of their relatives (2.3%) [10]. It is therefore not uncommon that a patient could make the diagnosis him or herself by searching the Internet. In most cases, diagnosis is made owing to changes in the face or extremities; in some other cases, acromegaly is diagnosed not for its signs and symptoms but during the biochemical exploration of a pituitary adenoma.

5.4.2 Symptoms

Acromegaly can cause a broad variety of symptoms [16].

5.4.2.1 Skin Changes

Nearly 70% of patients have sweaty and oily skin. Skin thickening is due to glycosaminoglycan deposition and to increased collagen production by connective tissue. These changes may lead to hyperhidrosis and malodorous sweating. Facial

wrinkles, nasolabial folds, and heel pads are increased in thickness, and body hair may become coarsened. Skin tags are frequent and may be a marker of colonic polyps. Raynaud's disease is present in one-third of cases. In some cases, patients describe night-time malodorous sweating.

5.4.2.2 Bone Changes

In response to both GH and IGF-I, new periosteal bone formation leads to an increase in skeletal growth, especially at the level of the mandible (prognathism). Jaw thickening, tooth separation, frontal bossing, malocclusion, and nasal bone hypertrophy are the standard facial bony deformities in acromegaly.

Radiography shows a thickening of the cranial vault and protuberances, frontal internal hyperostosis, and condensation of the *sella turcica* walls with clinoid hypertrophy. Hypertrophy of the sinuses, especially the frontal sinuses, is also clearly visible. This, along with laryngeal hypertrophy, may explain why the voice tends to become deeper and acquires a sonorous resonance [76].

These changes are not only due to soft tissue hypertrophy and excessive growth of bone and cartilage but also to bone deformation. Indeed, radiographic findings are abnormal in half of these patients, showing distal tufting of the phalanges, widening of the base of the phalanges with osteophyte formation, enthesopathy (mineralization of ligamentous insertions), widening of the cortical bone diaphyses, and widening of joint spaces due to cartilage hypertrophy. Deformations can also affect the rest of the skeleton, and dorsal kyphosis with distortion of the rib cage may be observed in severe chronic forms, leading to the paradigmatic “punchinello” aspect, especially when GH hypersecretion begins prior to epiphysis closure.

Bony deformations also affect the spine, with upper dorsal kyphosis and compensatory lumbar hyperlordosis. Vertebral enlargement, widened intervertebral spaces, and osteophyte formation were also observed. The thorax is deformed by protuberance of the lower portion of the sternum and by elongation and divergence of the ribs due to overgrowth of the chondrocostal joints.

Imaging studies show diaphyseal cortical thickening of the long bones and widened joint spaces, sometimes with osteophytes.

Concerning mineral changes, bone remodeling is increased in acromegaly [77, 78]. Cortical bone thickens (as measured by the metacarpal index and histomorphometric parameters) and its porosity is diminished. Trabecular bone mass may be decreased, normal or increased. Measurement of spinal bone mass can give contradictory results, probably because acromegaly is often associated with other endocrine disorders interfering with bone mass. In general, bone mass is normal in the lumbar spine in patients with isolated acromegaly but could be decreased in patients having other related endocrinopathies impacting bone metabolism, such as hypogonadism or hyperparathyroidism. Despite similar bone mineral density values, a lower lumbar spine assessed by the trabecular bone score (TBS) technique was demonstrated in patients with acromegaly compared to controls, especially in hypogonadal patients and women [79]. In a study [80] independent of BMD, the prevalence of vertebral fractures was found to be higher in patients with acromegaly (57.5% vs 22.6%). Fractures were associated with higher serum IGF-I values, a

longer duration of active disease, and a longer history of untreated hypogonadism. This higher prevalence of vertebral fractures persists despite biochemical control of acromegaly [81].

5.4.2.3 Rheumatologic Comorbidity

Peripheral Osteoarthritis

The topic has been reviewed in detail in [82, 83].

Peripheral joint symptoms are very frequent. Arthralgia and myalgia occur in 30–70% of patients. Among the sites, large joints such as the knees, shoulders, hands, wrists, and hips seem to be more affected. Acromegalic osteoarthritis develops within an average of 10 years after diagnosis.

Osteoarthritis develops in two stages. In the initial stage, the growth of joint cartilage and periarticular ligaments is stimulated, leading to enlargement and congestion of the interarticular space that limits mobility and induces joint pain; in the second stage, more degenerative changes of the joint geometry are observed: intra-articular microtrauma and exuberant repair reactions induce scars and subchondral resorption and osteophytotic development, leading to progressive joint deterioration. The pain is thus mainly mechanical, degenerative, and noninflammatory and often persists after treatment of acromegaly. However, rarely, some patients may present symptoms and signs of pseudoinflammatory osteoarthritis, which are dramatically relieved by the treatment of acromegaly. Joint mobility (especially of the shoulders) can be limited in the later stages of the disease. Joint effusion is rare, and synovial aspiration shows a generally degenerative picture with no evidence of inflammation; it may also reveal calcium microcrystals (associated chondrocalcinosis).

Physical examination of the joints often provides little information. The abnormalities are generally minor despite subjective functional discomfort. The shoulders and hips may show a loss of mobility and function. In contrast, some patients have joint hyperlaxity. There was no correlation between the presence or severity of osteoarthropathy and the age of onset of acromegaly or the mean GH or IGF-I concentration at baseline or during follow-up. Osteoarthritis appears to be more frequent after 45 years of age.

Radiological studies show a widening of the joint spaces, reflecting hypertrophy of the hyaline cartilage, as well as the presence of osteophytes, bone proliferation at the attachment sites of tendons and ligaments, periarticular calcium deposition, and exostosis of the bone. The joint space subsequently diminishes due to destructive arthritis. Sonography shows a thickening of the cartilage in the shoulder, wrist, and knee joints, which is improved with treatment for acromegaly.

Osteoarthritis inexorably progresses in advanced stages of the disease. It is not influenced by successful treatment of acromegaly, with the exception of diffuse articular symptoms and some sites of pain [84]. Acromegalic osteoarthritis considerably impairs patients' quality of life [85–87].

Spinal Involvement

The estimated prevalence of spinal involvement is approximately 40–50% [88]. Backache is more frequent at the level of the lumbar spine than the cervical or dorsal segments. The pain is mainly mechanical in nature, but inflammatory features can occur in later stages (16%). Spinal involvement may be accompanied by nerve compression. Occasionally, bilateral intermittent claudication reveals lumbar spinal stenosis. Pain may also be related to an increased prevalence of vertebral fractures despite normal BMD [80, 89].

Radiological examination shows typical features, including ossification of the anterior and lateral surfaces of the vertebral bodies, contributing to enlargement of their anteroposterior diameter, as well as a biconcave vertebral aspect and scalloping of the vertebral bodies (exaggerated concavity of the posterior vertebral wall). The mechanism of these morphometric changes is poorly understood but may involve hypertrophy of the intraspinal soft tissues (ligamentous hypertrophy, epidural lipomatosis) or bone. In more severe cases, ossification of the anterior surface of the vertebral bodies can bridge the disk space and give an aspect of diffuse idiopathic skeletal hyperostosis. An increased number of vertebral fractures with wedge deformity and thoracic kyphosis is also more prevalent in patients with acromegaly than in the general population [90].

5.4.2.4 Neuropathies

Symptomatic carpal tunnel syndrome is frequent. Nerve conduction studies have shown that the vast majority of patients with acromegaly have subclinical abnormalities of nerve conduction. Magnetic resonance imaging (MRI) shows a higher amplitude and intensity of the median nerve signal in patients with symptomatic carpal tunnel syndrome compared to asymptomatic patients [91]. The mechanism appears to involve median nerve edema more than extrinsic compression due to an excess of connective tissue, bone or synovial hypertrophy or an increase in extracellular fluid within the carpal tunnel itself with Schwann cell demyelination. Nerve edema, which can also easily be evaluated with ultrasonography [92], improves when GH and IGF-I levels fall, suggesting that hormonal control is a key prerequisite for improving these patients' neurological status. Sometimes, however, carpal tunnel syndrome may persist.

Ulnar nerve neuropathy at the cubital tunnel is also frequent in patients with acromegaly [93] and improves with treatment of acromegaly.

Apart from mechanical/compressive effects on nerves, autonomic nervous system dysfunction is present in patients with acromegaly, as shown by assessing the heart rate variability indices (mean sinus heart rate, RR intervals) and reverses after effective treatment [94].

5.4.2.5 Psychologic Consequences

Self-esteem may diminish along with progressive facial and bodily disfigurement. Patients with acromegaly further exhibit impairment in body image distortion, disruption in interpersonal relations, and social withdrawal anxiety [95].

Patients reported more negative illness perceptions than patients with acute illness but more positive illness perceptions than patients with other chronic diseases [96].

Nonetheless, direct unstructured interviews reveal an association between the diagnostic delay and the doctor–patient encounter and the experience of this disease, which is often described as catastrophic, both before and after the diagnosis [97].

It is unclear whether reported depression, mood swings, and apathy result solely from these physical changes or whether they are intrinsic high GH exposure central effects.

Acromegaly carries a significant lifelong burden for the affected patient. When evaluating health-related quality of life by means of dedicated questionnaires (such as the ACROQoL), it is clear that values barely normalize despite disease remission or cure [98]. All the biological, environmental, and biopsychosocial aspects of this burden have been extensively covered in a recent review by Biermasz [99].

5.4.2.6 Cardiovascular Manifestations

Arterial Hypertension

Hypertension occurs in 20–50% of patients. Its prevalence increases with time after the onset of acromegaly, as well as with GH level and age. Several concomitant factors are likely to play a role in the pathogenesis of hypertension in acromegaly. The chronic expansion of extracellular fluid volume (hypervolemia) leads to fluid retention, with plasma volume being 10–40% above normal. At the kidney level, increased renal sodium reabsorption at the distal tubule level is generally observed [100]. Body fluid expansion is related to enhanced epithelial sodium channel (ENaC) activity [1, 101, 102]. Hypertension can also result from endothelial dysfunction [103]. Neither renin-angiotensin aldosterone nor the sympathetic system appears to be involved in the pathogenesis of hypertension in this setting. Other contributors to the onset and maintenance of hypertension in acromegaly are also the increase in peripheral vascular resistance, insulin resistance and diabetes, and the development of obstructive sleep apnea [104–106].

Cardiomyopathy

Cardiac disorders are a consistent feature. Many lines of evidence, especially from experimental studies, point to the existence of specific cardiac disorders in acromegaly that are completely independent of coronary involvement (currently found in only a minority of patients) or valve disorders, diabetes, or hypertension [107, 108].

The first step of acromegaly-related cardiomyopathy mainly consists of myocardial hypertrophy of the interventricular septum and left ventricular posterior wall. This condition is initially asymptomatic, at least at rest. The assessment of initial cardiomyopathy is generally performed by means of cardiac ultrasound examination or magnetic resonance imaging (MRI).

Generally, left ventricle parameters are normal (concentric hypertrophy). Myocardial hypertrophy can occur in the absence of hypertension and even in young patients (<30 years), reflecting the impact of GH excess itself on the myocardium. Its prevalence is likely to be overestimated by echocardiography compared to MRI [109]. Hypertension further aggravates cardiac hypertrophy. Echocardiography and isotope studies show altered diastolic function (abnormal left and right ventricle filling) related to abnormal relaxation: parietal stiffness is, at least in part, probably linked to edematous infiltration of the ventricular wall [110] and perhaps also to a certain degree of fibrosis. Clinical symptoms such as dyspnea during exercise may be observed in patients who are asymptomatic at rest. Systolic function is normal if assessed by conventional methods. However, novel techniques such as two- or three-dimensional speckle-tracking echocardiography reveal, even at an earlier stage, an increased frequency of subclinical systolic impairment in active acromegaly [111, 112]. At later stages, hyperkinetic syndrome (increased cardiac index) is frequent.

Arrhythmias and/or conduction disorders may occur at any stage of acromegalic cardiomyopathy [113]. Their prevalence has long been underestimated in these patients. Ventricular premature complexes have been shown to frequently occur in patients with acromegaly. In one study, systematic 24 h Holter ECG recordings showed complex ventricular arrhythmias in 48% of patients compared to only 12% of controls [114]. Most of these arrhythmias are subclinical and persist despite successful treatment of acromegaly. Myocardial remodeling, hypertrophy, and fibrosis are all likely to play a role in their onset. However, recent studies did not confirm the high prevalence of dysrhythmias [115].

Congestive heart failure can occur if the cardiac disorders progress (if GH hypersecretion persists and, probably, if other risk factors such as diabetes, hypertension, and sleep apnea are also present). Functional signs first appear on effort before becoming permanent. At this stage, echocardiography shows variable degrees of cavity dilation. Fortunately, these severe forms are now far less frequent (prevalence 3%) [116].

A number of cardiovascular parameters improve during effective treatment of acromegaly, even if some changes appear to be irreversible in certain patients. In general, younger patients and patients with a relatively short history of acromegaly show better “recovery” (from diastolic disorders, myocardial hypertrophy, or systolic dysfunction) [71, 117]. In contrast, when dilated congestive heart failure occurs, cardiac function (especially systolic function) may show a short-term improvement [100], allowing some patients to survive or to avoid heart transplantation, but the longer-term prognosis is worse than that of patients with heart failure due to other causes (5-year mortality rate 37%) [116].

There is controversy surrounding the cardiovascular (ischemic) risk carried by patients with acromegaly [118]. An increased prevalence of hypertension, a history of diabetes mellitus and decreased levels of high-density lipoprotein, low-density lipoprotein, and total cholesterol were found in patients with acromegaly, leading to significantly higher Framingham risk scores than in controls [119]. Biomarkers of cardiovascular disease were also found to be altered in another study [120].

However, carotid atherosclerosis and carotid internal media thickening are not more extensive in patients with acromegaly than in nonacromegalic subjects [121, 122]. Importantly, no increase in the prevalence of coronary artery disease (assessed by different means, such as cardiovascular events, calcium scores, or myocardial scintigraphy) is found in patients with newly diagnosed acromegaly compared to the general population [123–127]. The reason for this apparent discordance between observed and expected coronary events is currently unclear. It has been suggested that the known atherogenic effects of hypertension, insulin resistance, and diabetes induced by GH excess are counterbalanced by some other cardioprotective factors, such as decreased endothelial and systemic inflammation [128–130].

Cardiac Valve Disease

Cardiac valve disorders are highly prevalent in patients with acromegaly and can, along with other cardiac abnormalities, also contribute to the onset or aggravation of heart disease in patients with acromegaly [131]. The risk of valve disease increases with time since onset [132]. Acromegaly-related cardiac valve abnormalities, which may be related to fibrotic changes, seem to persist after effective treatment of acromegaly [133]. Furthermore, no cabergoline-induced cardiac valve remodeling was observed.

5.4.2.7 Metabolic Complications

Physiologically, GH increases blood glucose levels, exerts a lipolytic effect, and promotes triglyceride hydrolysis into free fatty acids and glycerol.

GH excess leads to insulin resistance at the level of the liver or in the periphery, leading to fasting and stimulated hyperinsulinemia. The prevalence of type-2 diabetes mellitus (T2DM) in acromegalic patients is more or less constant across studies and ranges from 20% to 56%, depending on the series [71]. The weighted mean T2DM prevalence in individuals with acromegaly is approximately 27% when comparing data from 14 national registries [11]. As long as the compensatory increase in insulin secretion by pancreatic β cells counterbalances the reduction in insulin sensitivity, glucose tolerance remains normal. Impaired glucose tolerance occurs when insulin secretion is altered, followed by the onset of diabetes [134].

Acromegaly is associated with a decrease in fat mass (both visceral and subcutaneous) but an increase in intermuscular fat mass (which may contribute to insulin resistance) and lean body mass [135, 136]. A recent study found an increase in exercise-induced myokine irisin circulating levels in patients with acromegaly [137]. This increase was independent of the disease status. The consequences on either glucose metabolism or thermogenesis of these findings still need to be demonstrated.

Alterations in lipid metabolism are reported in 30–40% of patients with acromegaly. In uncontrolled disease, a typical lipid profile is found, characterized by increased levels of lipoprotein(a) and triglycerides and decreased levels of HDL cholesterol [138]. The course of lipid parameters (and other cardiovascular risk factors) may vary with the treatment modality after therapeutic control of acromegaly [139].

Hypercalciuria is frequent in patients with acromegaly and may be associated with an increased incidence of nephrolithiasis. It is related to an IGF-I-mediated and PTH-independent increase in calcitriol synthesis, which is responsible for both absorptive hypercalciuria and increased fasting plasma calcium linked to enhanced distal tubular calcium resorption [1, 140]. An increased prevalence of hyperparathyroidism is also observed in patients with acromegaly, either in the context of multiple endocrine neoplasia (see the above “5.3.3 Genetic Syndromes Associated with Acromegaly” section) or independently (phenocopy) as a usual sporadic hyperparathyroidism.

5.4.2.8 Respiratory Complications

Sleep apnea affects 60–80% of all patients with acromegaly at the diagnosis of acromegaly. Men seem to be affected more than women [141]. Sleep apnea is more likely to be sought in patients who snore (reported by 78% of patients with acromegaly) and in those with daytime sleepiness (51%) or morning fatigue and morning headache (16%). Sleep apnea may be a contributory factor in hypertension, cardiovascular disease, and even cognitive decline. In most cases, apnea is obstructive, but one-third of patients have central apnea. Obstructive apnea is linked to anatomical changes due to mandibular and maxillary growth, soft-tissue thickening (especially of the palate and uvula), and changes in the angles of the different bone segments, leading to hypercollapsibility of the posterior and lateral hypopharyngeal walls. Hypertrophy of the tongue also plays a role [142], as does hypertrophy of the submaxillary glands.

Changes in respiratory function are frequent but less well documented. Anatomical modifications of thoracic bones and cartilage (leading to profound changes in the geometry of the rib cage) and mechanical changes in thoracic elasticity and the inspiratory muscles can lead to ventilatory disorders. Respiratory muscle strength is also abnormal. Altered mechanical and energetic properties of some upper airway dilator muscles have recently been demonstrated [143]. The inspiratory time is shorter, and the breathing frequency may increase.

Patients with acromegaly often have an increase in their total lung capacity (81% of men and 56% of women), owing to an increase in alveolar volume. An obstruction is found in 20–30% of patients (small airway or upper airway narrowing). Subclinical hypoxemia may be present. No ventilation-perfusion mismatching has been demonstrated.

The apnea-hypopnea index improves during effective treatment of acromegaly, along with the obstructive apnea index and oximetry values [141, 142, 144]. However, while apnea can disappear in some patients whose acromegaly is cured, it may persist or even worsen (likely due at least in part to associated obesity [145]) in others who thus require nocturnal positive end expiratory pressure. The reevaluation of sleep apnea is thus useful even if patients are cured or well controlled after acromegaly treatment.

Vocal changes have been described in patients with acromegaly. A deepening of the voice and a low fundamental frequency are observed in the population with acromegaly [76]. Modifications of the laryngeal cords and muscles, as well as upper respiratory tract thickening, may be responsible for these findings. However, the

clinical consequences and the phonetic handicap related to these changes are not currently known.

5.4.2.9 Pituitary and Sellar Mass Effects

Headache is a very common symptom. In contrast with nonfunctioning adenoma, headache may be present even in patients bearing a microadenoma, thus reflecting a multifactorial genesis other than a direct adenoma-related compressive/expansive effect. In large tumors (macroadenomas or giant adenomas), low visual acuity and visual field defects may be observed in cases of suprasellar progression. Compression of the normal pituitary may also lead to anterior pituitary deficiency, which must be explored clinically and biochemically. Diabetes insipidus is never associated with acromegaly, except after neurosurgery or in the context of pituitary apoplexy [146].

5.4.2.10 Neoplasia and Acromegaly

Through the GH- and IGF-I-related promotion of cellular proliferation and differentiation, neoplasm and cancer risks have always been a major issue when dealing with acromegaly. *In vitro* and *in vivo* studies have shown a direct effect of GH or IGF-I in mediating cell proliferation. Pharmacological blockade of these targets in some cases allowed tumor inhibition in cell and animal models [147]. Despite these data on molecular biology, the link between GH excess and cancer risk in acromegaly is still unclear [147]. Although cancer-related mortality varies across studies, it seems that an excess of cancer and related mortality is present in patients with acromegaly with uncontrolled disease [148]. An overall cancer prevalence of 10% (any type, any site) is found in national registries collecting real-life data [11]. There is also some controversy regarding the incidence of each individual cancer type in patients with acromegaly.

Figures of colorectal cancer relative risk compared with the general population, initially widely overestimated at 10–20, are probably only 2–3 as per novel estimates [149–153]. There are various potential biological mechanisms that could explain the increased risk of colonic cancer in acromegaly: direct effects of GH and/or IGF-I; hyperinsulinemia; increases in IGFBP-3, IGF-II, and IGFBP-2 levels; altered bile acid secretions and local immune response; increased large bowel length; and obesity [150, 153]. Some authors claim that epigenetic alterations predispose patients with acromegaly to cancer development [154]. As colonic cancer may be the consequence of colonic polyp degeneration, many studies have examined the prevalence of colon polyps in patients with acromegaly. Prospective studies show that up to 45% of patients with acromegaly have colonic polyps, which are adenomatous in 24% of cases [155] and can arise in all parts of the colon. The acromegaly-associated colonic lesions seem to exhibit some peculiarities, such as larger, multiple, and more dysplastic adenomatous polyps than in nonacromegaly patients [150]. There is no clear correlation between GH or IGF-I concentrations and the incidence of colonic polyps. Colonoscopy guidelines for patients with acromegaly are controversial. The British Society of Gastroenterology [156] recommends performing a colonoscopy in patients with acromegaly by the age of 40. A subsequent examination should depend on the findings at the original screening and on the disease activity: screening every 3 years

in patients with a previous adenoma or with elevated IGF-I and every 5–10 years in those without adenomatous/dysplastic polyps or those with only hyperplastic polyps. Some technical difficulties may be encountered in patients with acromegaly because of the increased colon length [153].

Goiter is found in a large proportion of patients with acromegaly. Thyroid nodules have been found in nearly 60–70% of patients [157]. Multinodular goiter is autonomous in 10–20% of patients, sometimes causing patent thyrotoxicosis. Although thyroid nodules are in most cases benign, the risk of thyroid cancer has been found to be higher than that in the general population (odds ratio, OR = 7.9, relative risk, RR = 7.6), with a prevalence of nearly 4%. These findings were confirmed by a recent Finnish study [158]. Nevertheless, contrary to colorectal cancer, most studies about thyroid cancer contain recruitment biases, and the real incidence of thyroid cancer in acromegaly is still a matter of debate [153, 157, 159]. As is the case for colonic cancer, a relative overestimation of thyroid cancer may arise because of increased physician awareness for these tumors, as well as the large use of ultrasonography during the screening of comorbidities in acromegaly.

Neoplasms of the breast, lung, prostate, skin, soft tissues, brain, bone, and lympho-hematopoietic system, initially described in association with acromegaly, do not seem to be overrepresented in these patients [160]. There is therefore remarkable agreement among all experts and reported guidelines, pointing out that surveillance in relation to these cancer sites should follow the same recommendations as for the general population [161].

It is currently acknowledged that, along with other cancers and neoplasms, the description of cancer occurrence is probably overestimated because of enhanced proactive screening. Modern imaging techniques may detect subclinical lesions and therefore affect the incidence rates. Other benign lesions may be found at a higher prevalence in patients with acromegaly. A higher incidence of meningioma has been found when analyzing encephalic MRI in patients with somatotroph adenomas versus those with other cell-type pituitary adenomas [162].

5.5 Diagnosis of Acromegaly

The diagnosis of acromegaly is suspected on clinical grounds and is confirmed by a typical biochemical profile [2, 74]. Clinical diagnosis is suggested by typical disfigurement due to progressive acral enlargement and modification of the facial appearance. In the case of very low progression or clinical incertitude, it is sometimes useful to assess the evolution by comparing serial photographs over several years (Fig. 5.2). Deep learning approaches are currently going to be tested to assist semiology [163]. It is of note that the regions of interest of these tools using aprioristic algorithms are primarily the same as those used by clinicians [163].

IGF-I (with reference to the age-adjusted normal range), the main GH-dependent growth factor, is the screening test recommended for acromegaly, with the diagnosis being confirmed by a nonsuppressive level of GH after an oral glucose load, OGTT [161].

5.5.1 GH and IGF-I

The introduction of international standards has minimized GH variability, which was mainly due to the use of polyclonal or monoclonal antibodies recognizing a mixture of different molecular forms. Manufacturers were recently advised to calibrate their GH assay kits with the international standard (IS) 98/574 [164].

The latest assays allow the limit of quantification to be as low as 0.05 $\mu\text{g/l}$ with an interassay coefficient of variation (CV) of <20% [164, 165].

In most cases, GH levels are elevated, both at baseline and after OGTT [166]. GH levels in the population with acromegaly are inversely correlated with age, in which the youngest patients have the most elevated serum GH concentrations, and with the maximal tumor diameter [10]. Previous recommendations consider a diagnosis of acromegaly if nadir GH levels are above 1 $\mu\text{g/l}$ [74, 167]. However, a few patients with clear clinical signs of acromegaly and high IGF-I levels could have low GH output and can thus suppress GH levels to less than 1 $\mu\text{g/l}$ during the OGTT. Thus, a more stringent criterion of a nadir GH at 0.4 $\mu\text{g/l}$ after OGTT has been proposed [168] and is now increasingly recognized as the recommended threshold if a sensitive GH assay is used. This is in line with recent normative data in healthy subjects underlining the importance of sex, BMI, and the use of contraceptive (estroprogestative) pills in defining the threshold for GH under OGTT [169]. However, it must be emphasized that the last Endocrine Society guidelines continue to recommend the 1 $\mu\text{g/ml}$ threshold rather than the 0.4 $\mu\text{g/l}$ threshold, considering that in the United States, the use of ultrasensitive GH assays is not yet generalized [161]. A paradoxical increase in GH following OGTT is observed in approximately 10–30% of patients with acromegaly [170, 171].

For the IGF-I assay, the IS 02/254 WHO reference standard has recently become available. It is an ~97%-pure recombinant standard recommended for manufacturers [164, 165]. The IGF-I level increases in parallel to the log of the GH concentration and must be determined by using age-adjusted norms because levels fall with age. A multicenter cohort study comparing six IGF-I immunoassays in 911 healthy individuals showed good agreement at lower but not upper levels [172]. This variability, especially in upper levels, which are more interesting when evaluating the biologic control of disease, leads to a marked variability in each individual's IGF-I levels. Concordance between assay values in intraindividual patients with acromegaly was on average good (ranging from moderate to excellent) [173]. These differences in assay performances must be considered when evaluating disease control in subjects with acromegaly [173].

Similar to GH, IGF-I levels in patients with acromegaly are inversely correlated with age and with the maximal tumor diameter [10].

High IGF-I concentrations are also systematically found in other physiological states, such as pregnancy, puberty, and the postpubertal period. The concentration of IGFBP-3, the main IGF carrier protein, is usually increased in patients with acromegaly, but this marker offers little further diagnostic information in differential diagnosis.

GH and/or IGF-I measurements are of limited use for diagnosis (or treatment efficacy assessment) in patients with uncontrolled diabetes mellitus, chronic renal failure or pregnancy, and at the time of puberty.

Estradiol increases either basal GH or nadir GH levels after OGTT. This explains why GH is rarely inhibited by OGTT in women taking estrogen-containing pills. GH nadir concentrations are also significantly higher in lean and normal weight compared to overweight or obese subjects [169].

There are some individuals with a typical clinical picture of acromegaly but normal IGF-I and GH concentrations. This situation could correspond to two different situations: (1) spontaneously resolving real acromegaly, probably through necrosis or apoplexy of a previous GH-secreting pituitary adenoma; facial sequelae and disfigurement could have persisted despite the normalization of the somatotroph axis after spontaneous adenoma shrinkage; and (2) acromegaloid features may also be encountered in other diseases, such as severe insulin resistance, severe hypothyroidism, some forms of lipodystrophy, genodermatoses, or rarer overgrowth disease [174–176]. An extensive review focusing on various causes of pseudoacromegaly has recently been published [177].

Finally, some adenomas excised for mass effect or upon another surgical indication were revealed to derive from the somatotroph lineage only after histopathological examination [178]. In most of these cases, the somatotroph adenoma is silent, and no clinical signs of acromegaly are found. Nonetheless, subtle abnormalities revealing GH/IGF-I hypersecretion may be encountered [25, 179].

5.5.2 Neuroimaging

MRI is the imaging method of choice to detect a pituitary lesion. T1- and T2-weighted coronal and T1-weighted sagittal sections are routinely performed in diencephalic studies; gadolinium contrast usually shows a retardation in lesion enhancement demarcating the remaining hypophyseal tissue.

The majority of patients clearly have a pituitary macroadenoma (lesion above 10 mm). In patients with a sellar macroadenoma, once the diagnosis is established, before initiating treatment for acromegaly, patients must undergo a thorough work-up focusing on tumor mass effects (headaches, changes in the visual field and acuity, MRI abnormalities) and anterior pituitary function.

Although the majority of somatotroph adenomas are large tumors, in recent decades, the prevalence of microadenomas has seemingly increased in patients with acromegaly. It has to be known whether this trend depends on an improved clinical skill to detect disease (and therefore smaller lesions) or an intrinsic biological characteristic of somatotroph adenomas.

GH-secreting pituitary adenomas can be hypo-, iso-, or hyperintense on T2-weighted MRI sequences. Some authors suggest that hypointense imaging on T2-weighted MRI predicts a better outcome after somatostatin analog treatment either in terms of biochemical profile or tumoral shrinkage [180].

When MRI is contraindicated, a skull base CT scan may still be used. In patients with macroadenoma, this technique may show the presence of the pituitary mass and various extents of enlargement of the sella turcica.

Novel tools such as ^{11}C -methionine positron emission tomography seem to detect small pituitary remnants, especially those with a high metabolic rate and hypersecretion [181]. This technique seems particularly promising in equivocal MRI images [182]. Nevertheless, the accuracy of this technique has yet to be extensively established, and ^{11}C -methionine PET sequences are not routinely indicated in assessing pituitary imaging. Moreover, this technique is available in very few centers where a cyclotron is available on site due to the very short half-life of the radionuclide.

5.5.3 Pituitary Assessment

Associated prolactin hypersecretion is present in up to 30% of cases and may be either functional, secondary to impairment of hypothalamic dopamine production or compression of the pituitary stalk by the tumor, or due to a mixed adenoma.

In patients with microadenoma, no other pituitary defect or sellar mass effect is expected.

5.5.4 Total Body Imaging

If, despite an overt disease, no image is found on MRI, an ectopic GHRH secretion must be suspected and appropriate imaging requested [50].

Some occult neuroendocrine tumors may require total body scans (CT scans, MRI) or functional imaging (Octreoscan®, F-DOPA, or DOTATOC) [183]. Biopsy may help prove the neuroendocrine nature of these neoplasms. Complete excision of the underlying tumor usually cures disease.

5.6 Management and Follow-Up

Management of acromegaly is multimodal and quite consensual across different American and European guidelines and clinical practices [74, 165, 184–188].

The main aim is to relieve symptoms, normalize or decrease GH/IGF-1 excess, remove or reduce pituitary tumors, and improve long-term morbidity and mortality [185, 189]. Recent epidemiological studies have helped to refine the definitions of “cure” and “good disease control”, which are now far more precise: the GH concentration (in a random sample) must return to less than 1 $\mu\text{g/l}$ in the new sensitive assays that are now widely used (if the OGTT is used, the nadir needs to be less than 0.4 $\mu\text{g/l}$) and the IGF-I level must return to normal according to sex and age [165, 187]. A stepwise therapeutic strategy based on surgery and/or radiotherapy and/or medical treatment allows these goals to be achieved.

5.6.1 Neurosurgery

Surgery is generally the first-line treatment. Tumor excision, usually by the transphenoidal route, is the most rapid way of reducing GH and IGF-I concentrations in patients with acromegaly. Nevertheless, these levels normalize in only 40–70% of cases after surgery [11, 190–194]. The success rate depends on a range of features, such as the tumor size (microadenomas are more amenable to cure), the preoperative GH concentration (the success rate is higher when GH concentrations are <10 µg/l), and the surgeon's experience. Endoscopic techniques, now used in the majority of expert centers [195], though not improving the success rate, may attenuate local adverse effects [192].

Postoperative outcome in terms of symptom relief and biological disease control is generally assessed 3 months after surgery. When surgery fails to achieve disease control or when surgery is impossible or contraindicated, patients are offered radiotherapy and/or pharmacological treatments.

5.6.2 Radiating Techniques

Radiotherapy techniques have evolved over time, refining the techniques and number of sessions. Radiosurgery is a term used to define high-dose radiation delivery. It better applies to small targets and requires a single or few sittings. Fractionated radiotherapy refers to radiation therapy delivered at smaller doses but with multiple treatments (typically 25–30 sittings during 5–6 weeks). In order to minimize the dose to surrounding tissues, stereotactic localization is now used. Stereotactic radiosurgery (SRS) may use different radiating particles, such as photons (gamma knife, Linac, CyberKnife) or charged ions (protons). Stereotactic fractionated radiotherapy (SFR) is a hybrid form combining stereotactic localization with fractionated therapy administered by 3D-conformal radiation therapy, intensity-modulated radiation therapy, or proton radiation therapy [196].

Radiating techniques have consistently evolved over the last decade, from conventional radiotherapy to three-dimensional (3-D) conformal and stereotactic techniques. Technical improvements have been performed in all aspects of radiation treatment, including better imaging and 3-D planning, patient immobilization, sophisticated imaging systems for accurate patient repositioning and a more precise dose delivery, and reduction in normal surrounding brain structures exposed to high radiation doses [197].

In patients with somatotroph adenomas, normalization of GH/IGF-I levels occurs in approximately 40–60% of patients 5–10 years after treatment, with a 50% decline in GH and IGF-1 preradiation levels in approximately 2 and 5 years, respectively [190, 198, 199].

The choice between SFR and SRS, like for any other pituitary adenoma, in part depends on the size of the tumor and on its contiguity with the optic apparatus [200]. It is of note that the baseline GH concentrations predict treatment outcome

and the time-to-normalization of patients with high (>3–4-fold ULN) IGF-1 levels requiring up to 10 years to achieve biochemical control of disease [199, 201].

SRS provides more focused irradiation. In a French series of over 80 patients, the efficacy of gamma-knife irradiation was close to that of SFR [202]. In a recent meta-analysis, disease control (without complementary medical treatment) was achieved in 48–53% of cases after a mean follow-up of 4 years. The relatively larger figures by SRS are probably explained by the small size of tumors (2.1 ± 1.2 mL) [203]. Apart from disease control, the different SRS techniques give excellent results in controlling tumor growth, with >95% success according to different series [200, 202–204].

A recent review of the literature proved a similar rate of tumor control between stereotactic radiosurgery and SFR for patients with persistent active acromegaly after surgery and/or during medical therapy [205]. Tumors were stable or decreased in 93–100% of patients at 5–10 years, whereas endocrinological remission was achieved in 40–60% of patients at 5 years [205].

On the other hand, radiotherapy leads to variable degrees of anterior pituitary insufficiency in 50–100% of patients after 10–15 years, regardless of the technique. Complications such as radionecrosis and optic neuropathy are very rare. In contrast, the risk of stroke and cerebrovascular events may be increased, sometimes many years after irradiation [206]. When compared to patients not exposed to radiotherapy, stroke incidence appears to be increased from 1.7 to 2.8 times [200, 207]. Along with cortisol deficiency and inadequate hormonal substitution, these findings seem to account for the excess mortality in these patients [208]. The question of whether cerebrovascular risk may be lowered by newer radiating techniques is presently still unanswered.

5.6.3 Medical Treatment

5.6.3.1 Dopamine Agonists (DA)

Cabergoline appears to be the most effective among DA agents [209, 210]. In a meta-analysis of all published studies, IGF-I normalization was achieved in up to 34% of cases [211]. Multivariate analysis showed that the efficacy depended on the initial IGF-I concentration, the treatment duration, and the basal concentration of PRL (and, to a lesser degree, the dose of cabergoline) [211]. As in patients with hyperprolactinemia, cardiac valve disease does not seem to be increased in patients with acromegaly treated with cabergoline in the long term [133, 212].

Because of their dual origin, mixed lactotroph/somatotroph tumors are more likely to respond to DA [213]. Half of the patients with GH/PRL-secreting adenomas normalize their IGF-I levels, and 60% of those with macroadenomas display tumor shrinkage [209].

5.6.3.2 Somatostatin Receptor Ligands (SRLs)

SRLs suppress GH secretion by binding to somatostatin receptor subtypes (sst) sst2 and sst5, which are mainly present on somatotroph adenoma cells [214]. These

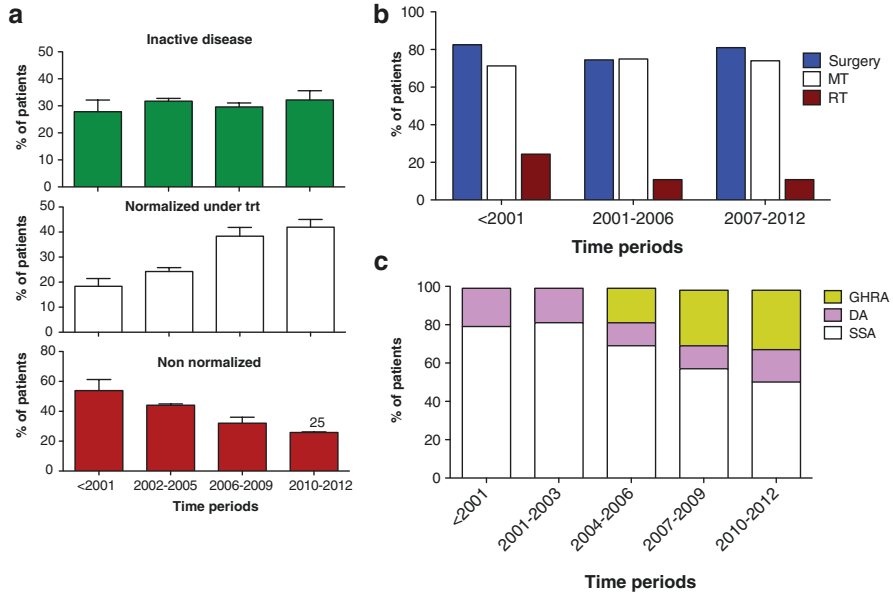


Fig. 5.5 Trends of disease control, treatment approach, and medical therapy over time in acromegaly—the example of the French Registry of Acromegaly. Panel **a**. Evolution of disease status across 4-year follow-up periods in the French acromegaly registry. Histograms indicate the percentages of patients and standard deviations; trt: medical treatment. Panel **b**. Distribution of treatment approaches in different follow-up periods. *MT* medical treatment, *RT* radiotherapy. Data are reported as percentages of patients. Panel **c**. Evolution of drug therapy in medically treated patients: somatostatin analogs (SSA), dopamine agonists (DA), GH receptor antagonist (GHRA). The histograms report the prescribed classes of treatment per patient according to different follow-up periods as the percentage of prescriptions. Note: Pegvisomant was approved for the treatment of acromegaly in France in late 2003. Adapted from [23], with permission

drugs have been demonstrated to exert either antisecretory or antitumoral effects (Fig. 5.5).

The first SRL to be marketed, octreotide (Sandostatin®), can be injected subcutaneously (SC), generally by the patient him/herself, at a dose of 100–200 μg two or three times a day [215]. Sustained-release SRLs (lanreotide and octreotide LAR) progressively followed and had an impact on the market due to their comfort. The former requires deep SC injections every 28 days at variable doses (Somatuline® Autogel® 60, 90, or 120 mg). The latter is administered intramuscularly once a month (Octreotide LAR, Sandostatin® LAR 10–20 or 30 mg). The dose and frequency of injections may be initiated and adjusted depending on the GH/IGF-1 concentration.

These SRLs bear similar efficacy [216] in driving GH concentrations below 2 $\mu\text{g}/\text{l}$ (60% to 70% of cases) and in normalizing IGF-1 levels (50–80%) [217, 218]. A recent meta-analysis has emphasized that control rates were highly variable from one study to the other. If clinical design characteristics had no statistically significant impact on efficacy determination, then later year of publication, study duration,

and prior somatostatin analog use were significant efficacy determinants for acromegaly trial outcomes. In that meta-analysis, overall achieved control rates were 56% for mean GH and 55% for IGF-1 normalization [219].

Several long-term studies have shown that the cure rate may improve over time [220–222].

In a handful of good responders, SRL injection frequency may be lengthened or even safely halted with no subsequent increase in GH/IGF-I concentrations [223, 224].

Tumor volume shrinks in a weighted mean of 37–51% of patients [225]. It seems that the reduction in tumor volume is larger when an SRL is used as first-line treatment [226]. When not shrinking, tumor volumes remain at least stable in the vast majority of cases [217].

SRLs may cause gastrointestinal disorders (abdominal bloating, nausea, diarrhea), which are generally transient. SRLs induce the occurrence of gallstones in 10–20% of cases that did not respond to ursodeoxycholic acid [227, 228]. Some practitioners prescribe pancreatic enzymes in SRL-related diarrhea. Changes in glucose metabolism are sometimes observed, including impaired glucose tolerance or even diabetes in patients who are overweight. In other cases, however, glucose tolerance improves following the reduction in insulin resistance due to the lowering of GH concentrations. Overall, according to recent meta-analyses, despite a decrease in fasting plasma insulin levels, no consistent changes in fasting glucose and HbA1c levels have been observed [229, 230].

Pasireotide (SOM230 or Signifor®) is a second-generation SRL compound that binds to sst1, 2, 3, and 5 with high affinity [231], which has been proven to be effective in controlling acromegaly [232–234]. When directly compared to octreotide LAR, pasireotide was able to control a higher proportion of patients (36% versus 21%) [232]. In a crossover study, 15% of noncontrolled patients under maximal octreotide doses responded to pasireotide [235].

Concerning the side effects, glucose metabolism abnormalities (diabetes or glucose intolerance) were far more frequent in patients receiving pasireotide than in those administered conventional SRLs [232, 233]. Gastrointestinal symptoms after pasireotide treatment seem to occur at a similar or slightly increased frequency [233].

This drug may be particularly interesting in patients with partial resistance to first-generation SRLs.

Among the factors believed to influence SRL effectiveness, there is the T2-weighted hypointense signal on MRI [236, 237], the presence of specific somatostatin receptor subtypes, and the aspect of densely granulated cells at histological examination [238].

5.6.3.3 GH-Receptor Antagonists

Pegvisomant (Somavert®) acts peripherally, blocking the effects of GH on its target organs by binding to GH receptors and by preventing their dimerization, GH signal transduction, and downstream activity, including IGF-I production [239]. As pegvisomant inhibits the action of GH but not its secretion, GH concentrations cannot be

used to evaluate treatment efficacy. IGF-I is used as a surrogate marker, together with clinical parameters. Pegvisomant is administered subcutaneously at a daily dose of 10–20 mg (sometimes more), with the dose being adapted to the hormone response (IGF-I normalization). Pegvisomant is highly effective, as IGF-I levels normalize in more than 90% of patients in the initial trials reported [240, 241]. In routine practice, the pegvisomant efficacy rate seems to be as low as 70% of cases, as shown by observational studies [242–247]. This treatment is reserved for patients in whom SRLs fail.

In a series of 304 patients in whom tumor volume was monitored for at least 3 years, an increase in tumor volume occurred in 9 cases within 8 months after commencing pegvisomant. This is likely related to rebound expansion after discontinuation of SRLs and/or to the natural history of aggressively growing pituitary tumors [248]; this latter situation may justify combination with an SRL to reduce tumor volume [249]. Tumor volume must therefore be monitored (by MRI) during this treatment. Available clinical data on pegvisomant concern a relatively small number of patients and relatively short treatment periods. Independent of disease control, pegvisomant improves glucose metabolism [250]. Adverse effects are limited to rare liver enzyme elevations, which are observed in between 2.5% and 3% of patients according to surveillance studies [242, 247]. Liver enzyme elevation generally normalizes either spontaneously or after treatment interruption. Exceptional cases of true hepatitis have been reported [246, 247]. Gilbert disease has been suggested as a risk factor for severe hepatitis [251, 252], but this was not confirmed by a recent Italian study [253].

SRL-pegvisomant combination therapy has also been developed [254]: a slow release formulation of the SRL is given once a month at the highest marketed dose (30 mg octreotide LAR or 120 mg lanreotide Autogel), and pegvisomant is injected once a week at escalating doses until the IGF-I level normalizes. IGF-I normalization was obtained in all patients with a median weekly pegvisomant dose of 60 mg [255]. This decreased dose requirement during combined therapy might be partially explained by an increase of approximately 20% in serum levels of pegvisomant [256]. Biochemical hepatic anomalies were quite frequent (although always transient) with this combination and appeared to be twice as common in patients with acromegaly with diabetes [257]. Compared with octreotide monotherapy, this combination appears to have a greater positive impact on quality of life for a given degree of IGF-I normalization [258]. This has raised the hypothesis of an extrahepatic effect of pegvisomant [259].

Cabergoline-pegvisomant combination therapy has also been proposed. In a multicenter, open-label, prospective clinical trial [260], the combination of cabergoline and low-dose pegvisomant (10 mg/day) was associated with a significant decrease in IGF-I levels compared with cabergoline alone, and 68% of patients achieved normalization. Then, when cabergoline was withdrawn and pegvisomant continued as monotherapy, only 26% of patients maintained normal IGF-I levels. The adjunction of cabergoline may be interesting when pegvisomant alone achieved minimally increased IGF-I levels [261].

5.6.4 Treatment Strategy

By analyzing large caseload series, several studies have evaluated medical practices and the evolution of treatment strategies over time [9, 11, 13]. The advantages, disadvantages, and costs of the different treatment options must be considered [262]. A marked evolution in clinical practice has been observed in recent decades (Fig. 5.5a–c).

An algorithm indicating a putative therapeutic strategy is proposed in Fig. 5.6. A surgical procedure is tried whenever possible. This depends on the availability of an

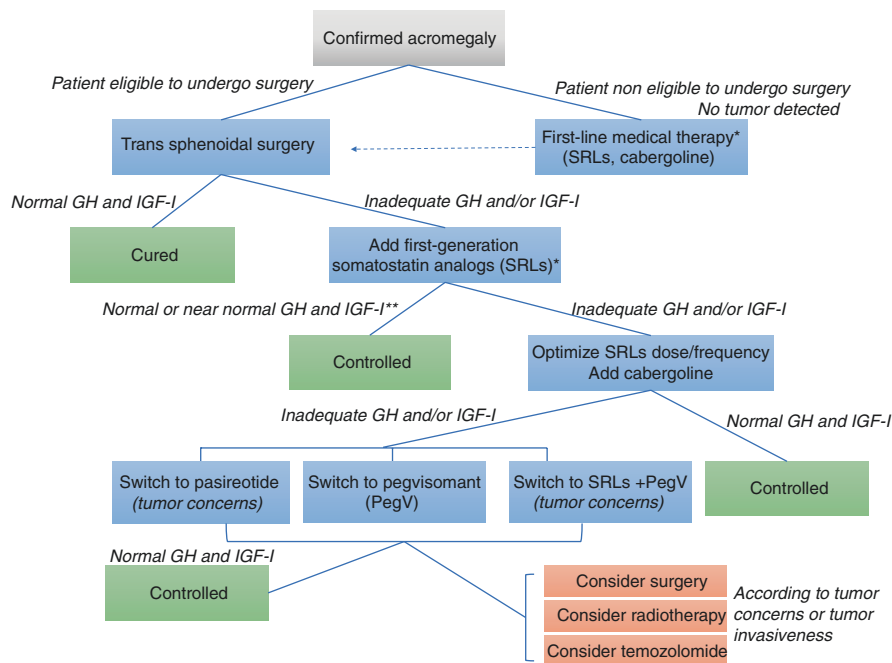


Fig. 5.6 Proposed algorithm of the treatment strategy for acromegaly. After confirmation of acromegaly, the first step is to establish the patient's eligibility for neurosurgery. In the absence of disease remission/cure after surgery, long-acting somatostatin receptor ligands (SRLs) are indicated. SRL doses and frequencies should be adapted and optimized, especially in partial responders ($\geq 50\%$ decrease in growth hormone (GH) and/or insulin-like growth factor 1 (IGF-I)). In the case of mild IGF-I elevation ($< 2\text{--}2.5$ -fold of the adjusted value for sex and age of the upper limit of normal value (ULN)), the addition of cabergoline can be considered. If disease control is not achieved, patients should be switched to the second-generation SRL pasireotide if there is clinically relevant residual tumor on imaging and/or clinical concern of tumor growth. Patients with impaired glucose tolerance should be switched to the GH antagonist pegvisomant (PegV). Patients with impaired glucose tolerance and tumor concern could be treated with a combination of a first-generation SRL and PegV. Patients who remain uncontrolled despite this second-line medical therapy should be discussed by a multidisciplinary team and considered for a second surgical intervention, a radiating therapy or temozolomide (features of aggressiveness, high Ki-67, tumor progression). *: consider using cabergoline in place of first-generation SRL if IGF-I elevation is $< 2\text{--}2.5$ -fold the ULN and/or in case of mixed GH/prolactin-secreting tumor; **:near-normal IGF-I is considered for IGF-I values < 1.3 ULN

experienced neurosurgeon, on the feasibility, on the fact that there are no anesthesiology constraints, and on the patient's choice. Surgery has been chosen in nearly 80% of cases, considering the weighted mean of 19 studies across different countries encompassing more than 16,000 patients with acromegaly [11].

In the case of surgery failure to cure acromegaly, medical treatment with SRLs is preferred as an elective option. SRL therapy is not only indicated after surgical failure but can sometimes be used for first-line treatment, especially when severe comorbidities create a risk of perioperative complications. Thus, when heart failure or respiratory problems are associated with acromegaly [71, 141], it is preferable to prepare the patient for surgery by administering SRLs for a few months first. In some cases, when a large tumor extends outside the *sella* and is not completely extractable by surgery, SRLs can be administered in the hope of controlling GH hypersecretion and tumor growth, thus avoiding the need for surgery [226, 263–267]. First-line SRL treatment before surgery has been chosen in 0–52% of cases, according to different series [11]. In these cases, when clinical conditions improve, neurosurgery could be performed as second-line treatment. According to a meta-analysis, IGF-I more likely normalizes after second-line treatment than after first-line drug therapy [218].

There is some controversy surrounding the ability of preoperative SRL therapy to improve surgical outcome: some studies [268–274] indicate that, in some patients with isolated somatotroph macroadenomas, surgery provides better control of acromegaly when patients are pretreated with an SRL, while other studies showed no difference [275–278]. Yang et al., in their latest meta-analysis, showed that preoperative SRL treatment was able to improve short-term (OR 2.07, 95% CI 1.50–2.87, $p < 0.00001$) but not long-term biochemical control [279].

The overall ability to normalize IGF-I by a first-line full-dose SRL (either octreotide LAR or lanreotide) is approximately 50% in recent series and the latest meta-analyses [280].

In some selected patients, especially in those with moderately increased IGF-I levels (below 2–2.5-fold the upper limit of normal) or in those with elevated concomitant prolactin levels, cabergoline may be tried first. It has indeed been shown that cabergoline is particularly useful in patients with low IGF-I excess [211].

After a first surgical approach, when full-dosed SRL therapy fails to achieve remission, several options may be chosen, mainly according to the patient status, his/her willingness, and the severity of clinical/biochemical disease persistence:

- (a) In the case of a large tumor remnant, it may be of utmost interest to repeat surgery. The main aim, in this case, will not be to cure disease but to debulk and decrease the secretory mass before trying medical treatment again [281, 282].
- (b) In the case of partial response to SRLs, physicians may choose to further adapt the adjusted doses [283, 284], to combine with other agents such as cabergoline [211], to administer pasireotide, or to initiate pegvisomant. When analyzing current anti-GH/IGF-I medical choices in these cases, a striking similarity is found between Germany and France, two countries where drugs are similarly available [9, 13]. In second-line treatment (after surgery failure), 60% of

patients have been treated with SRLs alone, 10% by a combination of SRLs and DA, 10% by pegvisomant, 8.6% by DA alone, 6.8% by SRLs and pegvisomant, 2% by DA and pegvisomant, and 2.7% by tritherapy (SRLs+DA + pegvisomant). Notably, at the time of the survey, pasireotide was not yet available in these countries.

- (c) In the case of full persistence or disease that is still clinically and biochemically severe, pegvisomant should be rapidly tried. Increasing doses may be chosen to improve symptoms and to normalize IGF-I levels. If possible, surgical debulking may also be interesting to propose for reducing the dose of pegvisomant necessary to achieve normal IGF-I.
- (d) Radiotherapy is far less chosen as the first or second line. Studies evaluating clinical practices over time show a remarkable reduction in radiotherapy use between <2001 and > 2007 (Fig. 5.5b) [9]. However, radiotherapy may be particularly interesting when aiming at avoiding remnant enlargement and controlling GH secretion. In the case of a small remnant, gamma- or CyberKnife could be proposed. In the case of large tumors, fractionated radiotherapy may be proposed to avoid further tumor enlargement. Apart from clinical and biochemical issues, the cost of these long-term medical treatments should be weighed against the risks of radiotherapy. In any event, medical treatment will be necessary while waiting for the benefits of radiotherapy to emerge.

All these treatments must be reassessed on a yearly basis. After radiotherapy, if medical treatment is necessary while waiting for the effects of irradiation, regular withdrawal is necessary for assessing the persistence of active disease.

5.7 Prognosis

Several targeted studies and meta-analyses have been conducted to explore mortality in populations with acromegaly. The overall body of evidence globally shows an increased mortality rate in patients with acromegaly [11, 285, 286].

According to the earliest series published in the 1980s–1990s, approximately 60% of patients die from cardiovascular disease, 25% from respiratory complications, and 15% from cancer. If untreated, patients with acromegaly have been reported to die approximately 10 years earlier than healthy subjects [5]. Several studies have shown that cerebrovascular disorders are a frequent cause of death, especially among women, but these studies involved patients treated in various ways (craniotomy, radiotherapy), many years ago, and a deleterious effect of these treatments (especially radiotherapy) cannot be ruled out [287, 288]. Two recent meta-analyses [286, 289] showed a standardized mortality ratio (SMR), i.e., the ratio of observed mortality in the population with acromegaly to expected mortality in the general population, of 1.72 (IC 95%, 1.62–1.83). However, recent reports describe a reduction in this trend, with mortality rates that seem no longer higher than the general population [290]. Bolfi et al. compared the mortality rates across 26 studies according to the date of publication of the series [285]. They found that the

mortality in acromegaly was increased from the 17 studies published before 2008, while no difference from the general population was found from the nine studies published after this date (SMR, 1.35; CI, 0.99–1.85). The posttreatment GH concentration is probably the best predictor of survival for all causes of death, independent of the type of complication. Thus, life expectancy outcomes can be stratified according to the posttreatment GH concentration: if GH secretion is controlled (<2 or 2.5 µg/l, or IGF-I normalization), life expectancy merges with that of the matched general population [287, 290, 291].

In the meta-analysis published by Holdaway and colleagues, it has been shown that the prognosis of acromegaly has improved in the last 20 years. This improvement is probably due to better disease control through a multimodal treatment strategy or to better management of comorbidities through improved awareness by physicians. Concerning the former aspect, a multimodal strategy and/or various anti-GH drug combinations witnessed a more aggressive treatment of the disease [9, 13, 292]. Concerning the latter, it is believed that mortality in acromegaly largely depends on the numerous and severe comorbidities. High GH/IGF-I concentrations, arterial hypertension, and cardiomyopathy are factors of poor prognosis, while the duration of symptoms and other factors (diabetes, lipid disorders, and cancer) are less important. Quality of life is also altered in acromegaly and is improved by effective treatment [293].

Finally, it must be stressed that, with the current therapeutic strategy, the vast majority of patients with acromegaly achieve very good control of GH/IGF-I secretion and have no problems related to tumor growth. Up to two-thirds of patients have normal IGF-I at the last visit, and these numbers seem to have increased in the latest series [11].

Adverse effects are infrequent and minor, even in the very long term. The figure is broadly different from the disease management 20 or more years ago, before the advent of somatostatin analogs. In addition, the use of more stringent criteria to define cure, together with aggressive treatment of comorbidities, has significantly improved the outlook of patients with acromegaly [118, 294]. However, even cured or well-controlled patients may have invalidating sequelae, such as joint pain, deformities, and impaired quality of life [145].

5.8 Conclusion

Acromegaly is a rare disease characterized by excessive GH and IGF-I exposure. In addition to the typical dysmorphic syndrome, a number of highly morbid diseases are associated with acromegaly. The cardiovascular, respiratory, rheumatologic and metabolic consequences and an increased oncologic risk represent the real burden of acromegalic disease and determine the prognosis. A detailed work-up of the various organs potentially involved in these complications is therefore recommended. Treatment is aimed at correcting (or preventing) tumor compression of neighboring tissues by excising the culprit lesion and at reducing GH and IGF-I levels to normal values. Selective pituitary sphenoidal surgery is often the

first-line treatment. When surgery fails to correct GH/IGF-I hypersecretion, a multimodal therapeutic strategy is available, including several medical treatment classes (standard and novel somatostatin analogs, dopamine agonists, or the GH receptor antagonist pegvisomant). Radiotherapy is currently proposed as a third-line treatment. The prognosis of acromegaly has improved in recent years: adequate hormonal control is achieved in most cases, providing a life expectancy increasingly similar to that of the general population. It remains to be shown whether the criteria used to define control of the disease in terms of mortality also apply to optimal management of comorbidities.

5.9 Learning Points

- Acromegaly, even if clinically manifest is diagnosed after a long delay which makes the cure of the disease more difficult and aggravates comorbidities.
- Preoperative GH level (high GH output) is an important predictor of remission in acromegaly.
- Persistent elevation of biochemical markers (GH and IGF1) following surgery indicates uncontrolled disease.
- Medical therapy nowadays is an important part of the treatment of patients with acromegaly.
- Age, size of the tumor, GH levels on presentation, histopathological type, and the somatostatin receptor status of the tumor in acromegaly may predict response to medical therapy.
- Despite the availability of multiple treatment modalities (surgery, radiotherapy, somatostatin analogs first and second generation, GH receptor antagonists, etc.), acromegaly sometimes is a challenging condition to treat.

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