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Guidelines

Position statement on the diagnosis and management of acromegaly: The French National Diagnosis and Treatment Protocol (NDTP)

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ABSTRACT

Acromegaly is a rare disease with prevalence of approximately 60 cases per million, slight female predominance and peak onset in adults in the fourth decade. Clinical diagnosis is often delayed by several years due to the slowly progressive onset of symptoms. There are multiple clinical criteria that define acromegaly: dysmorphic syndrome of insidious onset, symptoms related to the pituitary tumor (headaches, visual disorders), general signs (sweating, carpal tunnel syndrome, joint pain, etc.), complications of the disease (musculoskeletal, cardiovascular, pneumological, dental, metabolic comorbidities, thyroid nodules, colonic polyps, etc.) or sometimes clinical signs of associated prolactin hypersecretion (erectile dysfunction in men or cycle disorder in women) or concomitant mass-induced hypopituitarism

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Somatostatin analogues
Pasireotide
Cabergoline
Pegvisomant
Growth hormone
Somatotroph adenoma
Pituitary neuroendocrine tumor
Acromegalic arthropathy
Treatment
Diagnosis and care protocol

(fatigue and other symptoms related to pituitary hormone deficiencies). Biological confirmation is based initially on elevated IGF-I and lack of GH suppression on oral glucose tolerance test or an elevated mean GH on repeated measurements. In confirmed cases, imaging by pituitary MRI identifies the causal tumor, to best determine management. In a minority of cases, acromegaly can be linked to a genetic predisposition, especially when it occurs at a young age or in a familial context. The first-line treatment is most often surgical removal of the somatotroph pituitary tumor, either immediately or after transient medical treatment. Medical treatments are most often proposed in patients not controlled by surgical removal. Conformal or stereotactic radiotherapy may be discussed on a case-by-case basis, especially in case of drug inefficacy or poor tolerance. Acromegaly should be managed by a multidisciplinary team, preferably within an expert center such as a reference or skill center for rare pituitary diseases.

1. Introduction

The objective of the present National Diagnosis and Treatment Protocol (NDTP) – "*Protocole national de diagnostic et de soins* (PNDS)" in French – is to provide health professionals with an explanation of the current optimal diagnostic and therapeutic management and care pathway for a patient with acromegaly. The aim is to optimize and harmonize treatment and follow-up throughout France for this rare disease. This NDTP can be used as a reference by the patient's community physician in concertation with the specialist, notably to draw up a care protocol conjointly with the patient if a request for full insurance cover is being made for an unlisted disorder. However, the NDTP cannot exhaustively consider all specific cases, comorbidities and complications, therapeutic particularities, specific hospital protocols, etc., or replace the physician's individual responsibility to the patient. The protocol must also be updated in the light of new data. This NDTP for acromegaly was drawn up according to the NDTP methodology for rare diseases, published by the French Health Authority (HAS) in 2012, available at www.has-sante.fr. A more detailed document (in French) that comprises all the literature data analyzed (scientific argument), used as a basis for drawing up the Protocol, is available on the website of the HYPO reference center (http://fr.ap-hm.fr/site/defhy/pnds-du-centre-hypo/pnds-acromegalie).

2. Definition, epidemiology

Acromegaly is a group of clinical manifestations induced by chronic exposure to an endogenous excess of growth hormone (GH). Most often, acromegaly is related to GH production by a pituitary tumor. A few exceptional cases are reported to be due to the production of GHRH (growth hormon-releasing hormone) by a neuroendocrine tumor. Untreated, acromegaly induces significant excess mortality and morbidity, particularly cardiovascular and tumor-related. The presumed incidence of the disease is now estimated at 3.8 cases per million per year. There is no difference in incidence, age at diagnosis, or adenoma size between men and women. Prevalence is reported to be 60 cases per million, with a slight female predominance. The average age of diagnosis is 50 years, but prevalence increases with age. Acromegaly represents 9% of pituitary adenomas: i.e., the 3rd most frequent cause of pituitary adenoma, after non-functional and prolactinomas, linked in three quarters of cases to a macroadenoma. The novel concept of "micromegaly" is defined by a clinical phenotype of acromegaly associated with elevated IGF-I but normal GH concentrations. Acromegaly due to ectopic secretion of GHRH, which is very rare, is related to a pancreatic or pulmonary endocrine tumor (70% of cases) or sometimes to a hypothalamic tumor (glioma. . .). Acromegalogigantism, which is genetically determined in 50% of cases, is related to GH hypersecretion occurring before puberty, leading to tall stature. Pregnancy in women with acromegaly should be managed in a specialized center [1–9].

3. Diagnosis and initial assessment

3.1. Clinical diagnosis

Diagnosis is usually delayed by 5 to more than 10 years, as the specific dysmorphic syndrome progresses slowly. Early diagnosis is fundamental to limit complications, which can be irreversible, and to limit the severity of dysmorphic features, which has a major impact on quality of life. The dysmorphic syndrome is characterized by increased limb size, typical facies, and gigantism if onset is in childhood or adolescence. Other associated conditions include general signs (sweating, headache, asthenia, paresthesia of the hands, carpal tunnel syndrome, joint pain, etc.), signs of complications of the disease (see comorbidities), clinical signs of associated prolactin secretion in case of mixed adenoma and symptoms common to other pituitary macroadenomas (pituitary tumor signs: headache, chiasmatic repercussions and signs of pituitary insufficiency).

The dysmorphic features are the presenting symptoms, and also allow the diagnosis to be made. On average 3 to 4 doctors are consulted before diagnosis. The first doctors to make the diagnosis are endocrinologists, general practitioners, neurosurgeons, neurologists, internists, rheumatologists, ophthalmologists, dentists, etc.

Education of the various specialists (pulmonologists, ENT specialists, etc.) about the symptoms of acromegaly is fundamental for earlier diagnosis.

During the first diagnostic consultation(s), it is advised to propose consultation with a psychologist, inform the patient about patient associations, and to provide written material about acromegaly Fig. 1 [3,4,10,11].

3.2. Biological diagnosis

Biological diagnosis is based primarily on determination of IGF-I. Normal IGF-I concentration excludes the diagnosis of acromegaly.

Elevated IGF-I concentration (taking account of age and sex) is followed by GH determination on oral glucose tolerance test (OGTT). In general, GH on OGTT (75 g glucose) < 0.4 μg/L (or 0.2 μg/L in case of BMI > 25 kg/m^2) excludes acromegaly. In women, when applicable, OGTT should be performed on the last day without the pill or after estrogen treatment has been stopped for at least 6 days.

GH and IGF-I concentrations are positively correlated, but in some cases may be discordant in the same patient. These patients should be managed by expert endocrinologists who are aware of the analytical limitations of the assays [3,4,12–14].

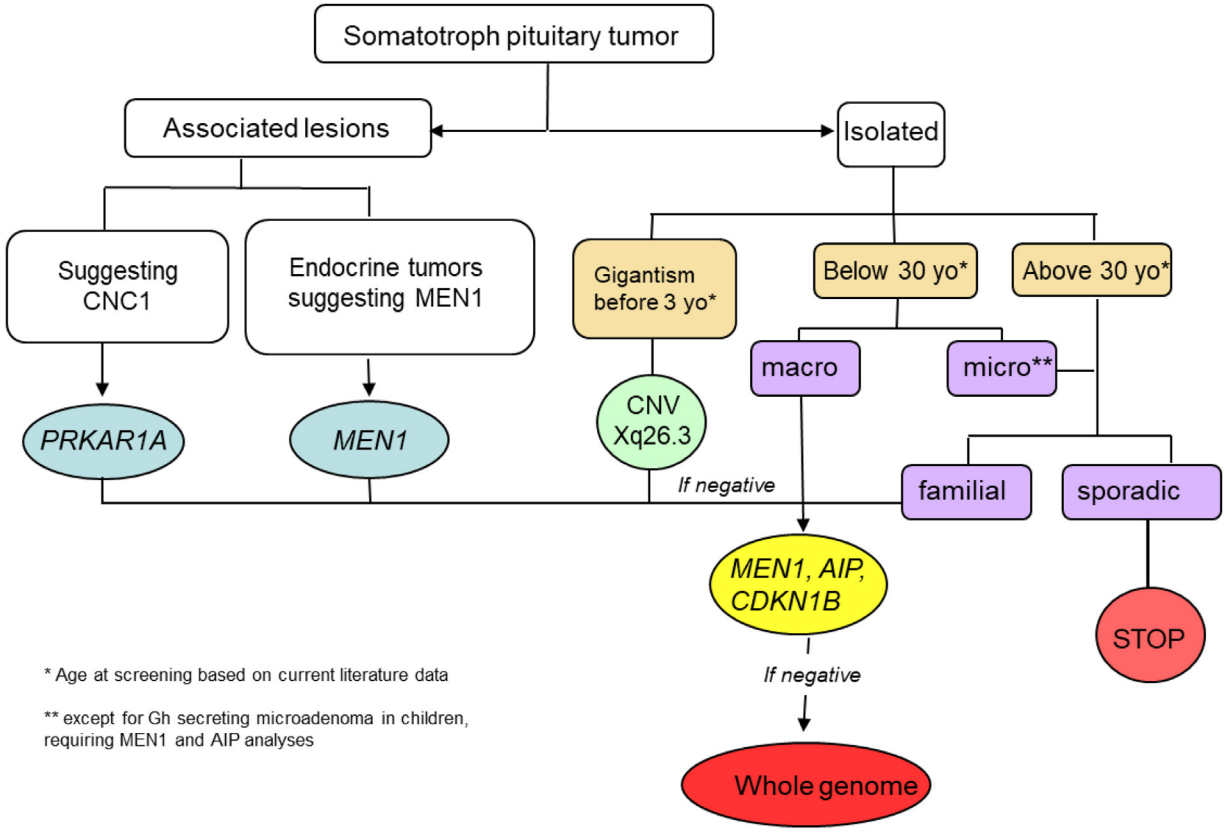

Fig. 1. Decision tree for molecular analysis in acromegaly.

3.3. Imaging diagnosis

Pituitary imaging aims to confirm the diagnosis of somatotroph adenoma, evaluate extensions and assess operability. MRI is the only technique that can be used. T2 sequences may also have some prognostic value by providing evidence for subtypes with differing treatment response.

The possible impact of the pituitary adenoma on the chiasma and optic nerves is analyzed on coronal sections, as is invasion of the cavernous sinus, which is easy to diagnose in the majority of cases, showing clear invasion. Invasion of the sphenoid sinus is very frequent, sometimes predominant, and well assessed on sagittal and coronal sequences.

A pituitary gland with a normal appearance on T1 sequences, before and after gadolinium enhancement, but hypointense on T2, in the presence of a typical acromegalic syndrome, should raise suspicion of a very rare pituitary hyperplasia linked to ectopic secretion of GHRH [9,15,16].

3.4. Genetic diagnosis

The genes involved in hereditary acromegaly are, in order of frequency, the *AIP* gene, pr more rarely the *MEN1* gene in the context of MEN1. Acromegaly in the context of Carney complex (*PRKAR1A* gene) or MEN4 (*CDKN1B* gene) is rarer and almost never occurs in isolation. Finally, some cases are associated with microduplication of chromosome X, always in a context of gigantism. Acromegaly in a hereditary context appears earlier than sporadic acromegaly, which explains the higher rate of gigantism. Of the patients with acromegalogigantism, 50% are carriers of a known genetic factor. The presence of a mutation in one of these genes can be used as a predictive test in relatives. This presymptomatic diagnosis is recommended from the age of 5 for *MEN1* and Carney complex, from the age of 10 for mutations in the *AIP* gene and from birth for Xq26.3 microduplication. Somatotroph tumors in this context of hereditary syndromes are often more aggressive and resistant to somatostatin analogues, requiring management by an expert center. Acromegalogigantism can also occur as part of McCune-Albright syndrome, a non-hereditary mosaic syndrome, and warrants IGF1 testing in all patients in whom this syndrome is suspected [7,17–23].

Since 2021, patients with suspected genetic origin of acromegaly and negative NGS on the appropriate gene panel can receive whole-genome study under the "France Genomic Medicine Plan" (*Plan France médecine génomique* 2025) after case discussion in a national multidisciplinary team meeting.

3.5. Histological diagnosis

The pituitary adenomas/pituitary neuroendocrine tumors responsible for acromegaly include several subtypes: "pure" somatotrophs, mixed somatotroph-lactotrophs and plurihormonal tumors of PIT1-lineage. Histopathological diagnosis of pituitary adenoma/pituitary neuroendocrine tumor is made by the pathologist on examination of surgical samples removed by the neurosurgeon. The histological aspect is consistent with a well-differentiated low-grade neuroendocrine neoplastic proliferation.

Proper typing and subtyping should be achieved by immunohistochemical staining for the hormones normally expressed in tumors of the PIT1-lineage (GH, prolactin and ß-TSH) and by cytokeratin expression pattern (perinuclear or "fibrous bodies").

An integrated approach to diagnosis is recommended, according to the clinicopathological classification described by J. Trouillas and colleagues in 2013: identifying the "invasive phenotype" on MRI evidence of invasive growth and the "proliferative histotype" defined by proliferation markers determines 5 degrees (1a, 1b, 2a,

2b, 3), useful to assess prognosis in pituitary adenomas, which can be implemented in the evaluation of these tumors [24,25].

4. Therapeutic management

4.1. Surgical treatment

Neurosurgical treatment of somatotroph adenoma, usually performed on an endoscopic transsphenoidal approach, by an expert neurosurgeon, is the only treatment (except for radiotherapy when indicated) that can be expected to permanently normalize growth hormone secretion.

Its effectiveness depends on the extent of the adenoma and the experience of the neurosurgeon: in experienced hands, according to a recent meta-analysis, the postoperative remission rate ranges from 78% in microadenoma to 53% in macroadenoma and 29% in invasive adenoma [26]. According to another meta-analysis, in "naive" patients, the efficacy of neurosurgery (65%) is higher than that of medical treatment (45%) [27]. Surgery seems to be interesting even when it leaves a remnant, as postoperative medical treatment of a somatotroph adenoma remnant appears to be more effective than medical treatment of a non-operated somatotroph adenoma [28–31].

Severe complications of surgery (severe intraoperative hemorrhage, meningeal breach) are very rare (0.6 and 1.2%, respectively), and pituitary deficit induced by surgery is rare (permanent diabetes insipidus 1.2%, new anterior pituitary deficit 8.7%). Recurrence rates after surgical remission have been estimated at 7% at 10 years [26,28,32,33].

We therefore consider neurosurgical treatment to be the first-line treatment for the majority of patients with acromegaly related to somatotroph adenoma. In microadenoma and macroadenoma without cavernous invasion, it can lead to cure. In macroadenoma with optic tract compression, it allows faster visual recovery than medical treatment. In macroadenoma with minimal invasion of the cavernous sinus, where complete resection can be expected with an expert surgeon, the value of preoperative medical treatment is controversial. Benefit was reported in series where results for less experienced teams were poorer than for more trained teams. In macroadenoma with clear invasion of the cavernous sinuses, surgery improves the efficacy of postoperative medical treatment, and is beneficial even if there is no compression of the optic pathways. However, in the latter case, it is certain that surgery does not enable remission and must be followed by medical treatment. It is therefore legitimate to test this medical treatment before surgery: if it allows good control of GH secretion then it is legitimate to continue without surgery [15,27,28,31,34–36].

As the effectiveness of neurosurgical treatment is highly dependent on the experience of the neurosurgeon, it is recommended that patients should be referred exclusively to experienced neurosurgeons in expert centers Fig. 2 [28,37].

4.2. Medical treatment

First-generation sustained-release somatostatin analogues administered by monthly injection (Octreotide LAR intramuscularly at 10, 20 or 30 mg or Lanreotide Autogel deep subcutaneous at 60, 90 or 120 mg) are the first-line medical treatment in acromegaly. The anti-secretory (40–75%) and the 50% anti-tumor efficacy of the two drugs as well as their tolerance profiles are similar: mainly transient abdominal pain, diarrhea, gallstones and blood sugar elevation [13,27–29,38,39] (Table 1).

Dopamine agonists can also be used, with less efficacy than in hyperprolactinemia and at higher doses: in practice, generally 2 mg to 4 mg/week of cabergoline tablets. Cabergoline alone normalizes IGF-I in 30–40% of patients, especially in cases of moderate hypersecretion (IGF-I below 2 times the upper limit of normal), sometimes with an associated anti-tumor effect. The most frequent side effects are dizziness, hypotension, nausea and drowsiness, justifying vesperal intake. The risk of inducing valvulopathy justifies transthoracic cardiac echography at the beginning of treatment, and the patient must be warned of the risk of addictive behavior [13,28,29,38–42].

In case of failure of first-generation somatostatin analogues, pasireotide LAR, a multi-receptor somatostatin receptor ligand (SRL) (second-generation SRL), can be prescribed in adult patients for whom surgery is not an option or has not been curative. With doses of 40 or 60 mg/month, normalization of IGF-I was observed in approximately 25% of patients previously uncontrolled by octreotide or lanreotide, with tumor reduction in some of these patients. The safety profile is comparable to that of octreotide or lanreotide, except for a higher frequency and degree of hyperglycemia. Hyperglycemia is observed more frequently in diabetic or glucose-intolerant patients (about 70%) than in patients with normal baseline blood glucose levels (about 40%), warranting special monitoring of blood glucose levels and patient education at treatment initiation [28,38,43,44].

The pegylated human growth hormone (GH) analogue pegvisomant is a GH receptor antagonist that decreases IGF-I, without direct anti-proliferative effect. The drug is self-administered by daily subcutaneous injection. In the initial studies, at a mean 20 mg per day, normalization of IGF-I was achieved in $\geq$ 90% of cases, and in observational studies in about 70% at 10 years. The theoretical maximum dose of 30 mg/d may need to be exceeded to achieve IGF-I normalization.

The impact of pegvisomant on carbohydrate metabolism is favorable or neutral, and the most frequent side effects are skin reactions at the injection site or liver cytolysis, which is usually spontaneously reversible and asymptomatic [45–49].

Several new treatments for acromegaly [38,50–52] as well as new formulations of somatostatin analogues are currently being tested in human clinical trials, including an oral form of octreotide, antisense oligonucleotides that block growth hormone receptor transcription, and a non-peptide somatostatin analogue that blocks receptor internalization.

4.3. Indications for medical treatment

Medical treatments are most often proposed for patients whose GH hypersecretion and/or tumor volume could not be controlled by surgical removal.

Preoperative medical treatment consists in administering somatostatin analogues for a few months, generally 3 to 6–12 months before surgery, in order to facilitate the surgical procedure and reduce perioperative complications. Some studies reported improved postoperative remission rates, particularly in certain cases of macroadenoma, while others showed benefit only in the case of surgery by a non-expert neurosurgeon. The interest of such an approach being controversial, it must be assessed on a case-by-case basis, ideally in a multidisciplinary meeting in an expert center [13,28,34–36,53,54].

A combination of two drugs with different mechanisms of action can sometimes be used to improve efficacy or reduce the side effects associated with each, reduce the dose or frequency of administration, and improve compliance. For example, somatostatin analogues can be combined with cabergoline, but also somatostatin analogues (or cabergoline) and pegvisomant [38,55–57]. In the latter case, the addition of pegvisomant (even with a regimen of 2–3 injections per week) may allow normalization of IGF-I in patients previously uncontrolled by somatostatin analogues [13,38,55,58,59].

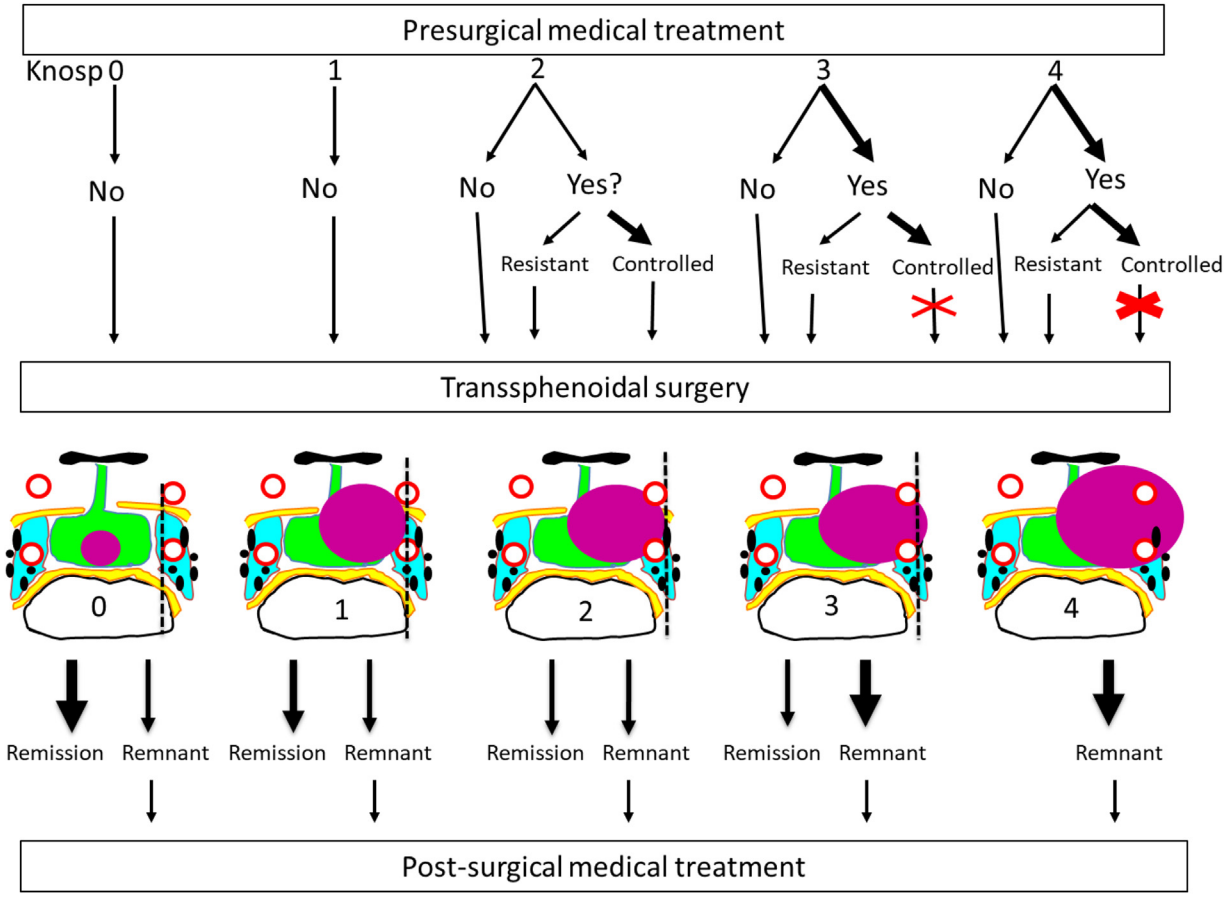

Fig. 2. Surgical indications in somatotropic adenomas based on cavernous sinus invasion (Knosp grade).

Table 1
Drugs available in France for the treatment of acromegaly.

Drug treatment	Laboratories	Doses	Dosage	Half-life	
1st generation somatostatin analogues	Octreotide	Novartis	10, 20, 30 mg powder and solvent for IM injection (sustained release)	One injection every 4 weeks of 10 to 40 mg	The concentration rises and reaches a plateau around day 14 then remains constant over the 3 to 4 weeks.
	Lanreotide	Ipsen Advanz Pharma	60, 90, 120 mg pre-filled syringe for SC injection (sustained release)	One injection every 4 weeks (3 to 6 weeks for 120 mg)	23.3 days (60 mg) 27.4 days (90 mg) 30.1 days (120 mg)
2nd generation somatostatin analogue	Pasireotide	Recordati rare diseases	10, 20, 30, 40 and 60 mg powder and solvent for IM injection (sustained release)	One injection every 4 weeks	The apparent half-life is about 16 days
Growth hormone antagonist	Pegvisomant	Pfizer	10, 15, 20 mg powder and solvent for SC injection	One injection per day of 10 to > 30 mg[a]; (possibility of 2 to 3 injections/week)	74–172 h
Dopaminergic agonists	Bromocriptine	Mylan	2.5 mg tablets 5, 10 mg capsules	2.5 mg to > 10 mg[a] in 3 doses per day	Two half-lives: 6 h and 15 h
	Quinagolide	Ferring	25 µg/50 µg, 75 µg, 150 µg tablets	25 to > 300 µg[a]/day in 1 dose/day	11 h
	Cabergoline	Pfizer Teva	0.5 mg tablets 0.5 mg tablets	1 tablet per week to > 1 tablet[a]/day	79 h to 115 h

[a] According to investigator's judgement based on tolerance, efficacy and cost, with limitations depending on local regulations.

In case of pregnancy, it is recommended that somatostatin analogues or pegvisomant be discontinued in advance, but cabergoline may be continued if necessary; reoperation is exceptional (severe headache or tumor growth) [8,28,29,39].

In children, cabergoline and somatostatin analogues can be used, although efficacy is less frequent than in adults; in case of ineffectiveness, pegvisomant alone or in combination can be proposed [13,60].

4.4. Radiotherapy

Radiotherapy and radiosurgery techniques have evolved over the last twenty years, with better target accuracy and lower toxicity in adjacent structures, leading to improved efficacy and reduced toxicity. Radiotherapy and radiosurgery use different techniques, with different patient profiles: for example, radiosurgery should be preferentially used for small lesions at sufficient distance from the optic pathways. Choice of modality must be determined in the framework of an expert center and according to the techniques available locally. The main indication is failure of pituitary surgery with ineffectiveness or intolerance of drug treatment. However, radiotherapy can also be curative, to stop long-term drug treatment, or to control tumor volume. Efficacy data show cure in about 50% of cases in terms of secretion, with maximum efficacy observed in 3 to 5 years after treatment (requiring drug treatment to control hypersecretion in the meantime). In radiosurgery, there is a risk of late recurrence in 10–20% of cases. Tumor control is achieved in 70–100% of cases, regardless of the modality. The main side effect is permanent hypopituitarism, in 10–80% of cases, with increased risk during follow-up. Other rarer side effects have been reported in the longer term: stroke, cognitive disorder, and radiation-induced tumors. Very long-term monitoring is therefore necessary for all patients, in terms of both hormones and long-term side effects [13,28,61–65].

4.5. Therapeutic education

Therapeutic patient education (TPE) is an integral part of the management and care of patients with a rare endocrine disease such as acromegaly. In these patients, the aim of TPE is to help them acquire or maintain the self-care and coping skills they need to manage their life with a chronic disease, improve their quality of life and succeed in their life projects. This program can be offered at any point in the patient's care pathway.

There are various TPE programs targeting pituitary pathologies in French national reference and skill centers. Without being specifically focused on acromegaly, they also include patients with this rare endocrine pathology. Multiple information documents are also provided to patients (on-line or paper format).

Participation in a TPE program can help acromegalic patients maintain or improve their quality of life, and can be very beneficial in living with and managing the disease and its consequences. These workshops allow the patient to get free of their isolation and meet other patients suffering from the same disease. Exchanging views on daily life, managing fatigue and pain, or even relationships with family members, meeting patients at different stages of the disease and treatment all enable better understanding of the disease, putting things into perspective, regaining self-confidence and confidence in the future, all of which often contribute to an improvement in self-esteem. It can also be interesting for relatives to participate, and to involve patient associations and expert patients [26,66,67].

4.6. Follow-up

The follow-up of patients with acromegaly must be carried out in cooperation with a pituitary reference or skill center, and the frequency of consultations must be adapted to the situation of each patient (at least once a year), in conjunction with the general practitioner.

Remission criteria have been revised over the past decades to become more and more stringent. The 2018 consensus defined biochemical control as GH nadir < 0.4 μg/L after OGTT using ultrasensitive assays and normal sex- and age-matched IGF-1 measured at least 12 weeks after surgery [28]. Long-term recurrence may be observed [33].

4.7. Long-term follow-up is essential, regardless of treatment modality

After surgery, postoperative evaluation, including IGF-I and GH measurement under OGTT and pituitary MRI, must be carried out at least 12 weeks after the operation. The visual field should be reassessed postoperatively if it was impaired preoperatively. If, at the end of this exploration, the adenoma is considered cured, long-term monitoring will remain necessary, with IGF-I assay at 3 months, 6 months and then every year. In pure somatotroph adenoma, MRI is not necessary as long as IGF-I is normal. If postoperative hormonal exploration is doubtful, close prolonged monitoring is necessary, with GH and IGF-I measurements every 6 months for the first 3 years and then annually. If the patient is not cured, complementary medical or radiotherapy treatment is usually proposed, depending on context [28,33,68,69].

After radiotherapy MRI imaging should be performed at 6–12 months and then annually at 2–3 year-intervals when the residue is stabilized on two successive MRI scans. Spaced surveillance of imaging is maintained in the very long term, given the low risk of a second tumor. GH/IGF-I measurements should be performed 6–12 months after irradiation and then annually. In patients treated medically while awaiting the effect of radiotherapy, therapeutic windows of 1 to 3 months are carried out at regular intervals for 1 to 2 years and over the long term, to re-evaluate the effect of the radiotherapy per se on GH secretion. Anterior pituitary hormone exploration should be performed between 6–12 months after irradiation and then once a year for 10–15 years. An ophthalmological check-up should be carried out annually if the tumor residue is in contact with the optic pathways [13,62,63,70–73].

4.8. Under medical treatment

4.8.1. 1st and 2nd generation somatostatin receptor ligands (SRLs)

Biological monitoring is based on repeat GH and IGF-I measurements at 3, 6 and 12 months at the start of treatment and then every year for as long as the treatment is continued. Monitoring of tumor remnants is carried out by MRI at 6, 12 and 24 months. Thereafter, there is no reason to repeat the MRI as long as the IGF-I is normalized, in the absence of tumor syndrome. Long-term monitoring includes annual clinical and metabolic evaluation. Glycemic monitoring must be particularly careful with second-generation SRLs [13,28,29,38,39,44,68,74–77].

4.8.2. Dopamine agonists

IGF-I assay every 6 months. The frequency of MRI monitoring is the same as for SRLs [13,28,40–42]. Cardiac echographic monitoring should be performed as needed [41].

4.8.3. GH receptor antagonist

IGF-I measurement every 6 months. Monitoring of injection sites (lipodystrophy) is essential. Imaging monitoring of any tumor residue is necessary every two years [46,78].

4.8.4. Conclusion

Long-term follow-up includes monitoring treatment efficacy and adverse effects, as well as monitoring the complications of acromegaly itself, which must be continued life-long because the associated comorbidities have a significant impact on the patient's health and quality of life. A network of specialists with knowledge

of the disease is very useful to help with this management, and to avoid loss to follow-up [10,28,79–81].

5. Management of comorbidities

5.1. Endocrine complications

Many patients with acromegaly have pituitary hormone deficits related either to compression of the hypothalamic-pituitary region by the tumor, to the consequences of tumor treatment (surgery, radiotherapy), or to a combination of the two. These hormone deficiencies should be treated by hormone replacement according to the guidelines [82]. Their detailed description is beyond the scope of this NDTP and has been developed in the NDTP on congenital hypopituitarism:

- corticotroph deficiency should be remedied mainly by oral hydrocortisone, with education of the patient on what to do in case of decompensation or in case of stress and intercurrent disease;
- thyrotroph deficiency is remedied by oral levothyroxine, to be adjusted mainly on the basis of T4 and T3 measurement rather than TSH value;
- gonadotroph deficiency is remedied by peripheral hormones: testosterone (generally in intramuscular injections every 2 to 4 weeks) in men or hormonal replacement therapy (HRT) containing estrogen and progesterone/progestin in women until the physiological age of menopause. Fertility treatments need gonadotropin injections;
- somatotroph deficiency can sometimes be managed by replacement in adults after recovery from acromegaly.

5.2. Respiratory complications

Sleep apnea syndrome, a very common complication of acromegaly, affects 47 to 87% of patients. In more than 85% of cases it consists in obstructive sleep apnea syndrome (OSA), related to a reduction in upper airway size (macroglossia, retropositioning of the tongue secondary to changes in the mandible, infiltration of the mucous membrane of the upper airway walls, increase in the thickness and length of the soft palate) and to functional abnormalities (impaired genioglossus contraction and increased collapsibility of the oropharynx). More rarely it is a central sleep apnea syndrome related to a GH-dependent increased ventilatory response to CO_2 or heart failure. The symptomatology of OSA is not different from that encountered in the general population with nocturnal signs (snoring, respiratory pauses, sweating, polyuria) and diurnal signs (daytime sleepiness, morning headache, asthenia, attention disorder, mood disorder, decreased libido), some of which are the same as those of acromegaly. Given the frequency of OSA, all acromegalic patients should undergo polysomnography, a reference examination diagnosing OSA and evaluating severity. The diagnosis is accepted if, in the presence of suggestive clinical signs, apnea-hypopnea index (AHI) is > 5 events per hour. OSA is considered severe if the AHI is > 30, and moderate for AHI 15–30.

The effect of hypersomatotropism treatment on the evolution of OSA is variable, with reports of improvement, no change and, more rarely, worsening. A recent meta-analysis nevertheless showed a significant reduction in nocturnal respiratory disorder, essentially during the first year of treatment, correlated with reduction in tongue volume. Nevertheless, OSA persists in 20–40% of cases, notably when severe initially. If OSA is severe and/or the clinical impact is significant, continuous positive airway pressure (CPAP) is introduced at diagnosis. The value of continuing CPAP ventilation should be re-evaluated some time after treatment of hypersomatotropism, with a polysomnography performed at least 72 hours after stopping CPAP ventilation. In the case of more moderate OSA, polysomnography after several months of hormonal control allows reassessment of the persistence of OSA and of the need for CPAP ventilation [83–88].

5.3. Cardiovascular complications

Chronic hypersecretion of GH and IGF-1 in acromegaly is accompanied by numerous functional cardiovascular consequences. Hypertension occurs in approximately 20 to 30% of patients. Pathogenesis is primarily related to increased plasma volume secondary to renal fluid retention, but abnormalities in vascular architecture and reactivity also play a role. Cardiac involvement is usually moderate or absent in early forms of acromegaly, and becomes more common in advanced forms poorly controlled by treatment. In addition to the direct effect of GH and IGF-I on the myocardium, it reflects the impact of hypertension, sleep apnea syndrome, overweight and diabetes. Left ventricular hypertrophy and diastolic dysfunction have been frequently reported in studies based on cardiac ultrasound and are usually minimal and without clinical consequences. More recent studies assessing cardiac structure and function on MRI reported much lower incidence of myocardial hypertrophy than echocardiography-based analyses. Progression to systolic dysfunction with congestive heart failure is now very rare. The risk of arrhythmia and clinically significant coronary heart disease does not appear to be increased, despite an increased prevalence of conventional cardiovascular risk factors. Valvular abnormalities are related to fibrotic changes in the valves and appear to persist despite effective treatment of acromegaly. Treatment with cabergoline does not appear to increase the incidence of valve disease. Advances in the treatment of acromegaly over the last few decades have significantly reduced associated cardiac morbidity, and cardiovascular complications are no longer the leading cause of death in acromegaly [4,33,80,89–93].

5.4. Maxillofacial complications

Soft-tissue involvement leads to thickening of the wrinkles and lips and enlargement of the nose. Tongue hypertrophy may be associated with intubation difficulties. Bone involvement results in dysmorphic growth of the facial bones: hypertrophy of the frontal humps, orbital arches, frontal sinuses and bony projections, and increase in facial height and bizygomatic diameter. There is also prognathism with prominent chin.

It is advisable to wait for one year of biological stabilization before considering maxillofacial treatment, if the patient so wishes. Bimaxillary surgery and glossoplasty can be discussed to rectify esthetics without restricting lingual space.

Odontologically, gingival hypertrophy, hypercementosis or tori are reported, as well as the appearance of interdental spaces and occlusal disorder due to mandibular growth. The management of this condition does not differ from conventional treatment. However, hypercementosis should be systematically investigated in case of dental avulsion [80,94,95].

5.5. Rheumatological complications

Musculoskeletal manifestations in acromegaly are common. They may be inaugural or occur during the course of the endocrine disease, whether active, controlled or cured by treatment. Their proper diagnosis by the endocrinologist, or even the treating physician, is essential as it is required to identify and monitor them and refer the patient to the rheumatologist. In practice, musculoskeletal damage should be mandatorily added to the list of comorbidities and manifestations of GH/IGF-1 hypersecretion. Musculoskeletal damage is due to the effects of GH and IGF-1 on bone, cartilage and

capsulotendinous tissue. IGF-1 has a trophic effect on peripheral nerve trunks, leading to hypertrophy and mechanical impingement.

Carpal tunnel syndrome, often bilateral, occurs early and must be diagnosed, but has often already been operated on. Ulnar nerve compression at the elbow joint should be considered.

Arthropathy is probably the most important cause of morbidity and functional disability in acromegaly. It affects all joints. When diagnosed late, osteoarticular sequelae cannot be modified by treatment. Specific management is necessary to improve quality of life.

Imaging on standard X-ray should be systematic and repeated to monitor initial clinical or radiological damage. Comparative X-ray of the shoulders (AP with 3 rotations), hips (pelvis upright, AP and false profile) and knees (AP upright, schuss, lateral and 30–60° patellofemoral) are recommended.

Spinal deformities are classic secondary to acromegaly. They contribute to dorsal kyphosis and lumbar hyperlordosis. Spinal pain and peripheral neurological compression are common. Standard X-ray can disclose specific changes such as scalloping of the posterior wall of vertebral body, increased length and dystrophy mimicking vertebral body fracture. Therapeutic management is the same as for any spinal pain and common neuralgia.

The consequences for bone are reassuring. Excessive IGF1 and GH secretion leads to increased bone remodeling promoting bone formation. There is no definite evidence of fracture related to acromegaly itself, but secondary panhypopituitarism and menopause can trigger bone loss and fragility, possibly leading to fracture. In case of fracture or densitometric osteoporosis, treatment modalities are those of postmenopausal osteoporosis, to which is added control of acromegaly [80,81,96–102].

5.6. Ophthalmological complications

The visual repercussions of pituitary macroadenoma classically include chiasmatic damage, first of all with damage to the upper visual fields and bitemporal hemianopia before a fall in visual acuity. The more anterior attacks cause defect of the central fibers on one side and inferior nasal fibers on the other, and the more posterior attacks cause homonymous defect. Oculomotor damage may be observed in case of apoplexy; very rarely, more serious damage occurs in case of compression of the third ventricle, with clinical intracranial hypertension and macular edema.

Visual assessment at diagnosis and every 6 months thereafter includes ophthalmological clinical examination with visual acuity measurement, intraocular pressure measurement, screening for ptosis or oculomotor palsy, and fundus examination for papillary pallor. An automated or Goldmann visual field examination is performed, typically to detect bitemporal hemianopia or quadranopia. Optical coherence tomography (OCT) is frequently performed to quantify any macular or papillary axon loss. In the postoperative period, ophthalmological consultation is recommended at 3 months, and then generally every 6 months in case of anomaly, with the help of the above-mentioned complementary examinations. In case of stability, monitoring can then usually be spaced out to an annual ophthalmological consultation. Regular ophthalmological consultations help eliminate differential diagnoses and associated pathologies (glaucoma or strong myopia, cataract).

The duration of optic compression, age, tumor size, optic atrophy and the intensity of the preoperative campimetric deficit are factors for poor prognosis. OCT with measurement of RNFL (retinal nerve fiber layer) and GCL (ganglion cell thickness) is an interesting tool, but has yet to be evaluated as a predictive of visual recovery [13,103–105].

5.7. Gastroenterological complications

The incidence of colorectal cancer in acromegalic patients is about twice that in the reference population. Location is mainly in the right and transverse colons. Colonic polyps are present in 27–55% of acromegalic patients and increase in number with age. It is recommended that the first colonoscopy be performed at diagnosis for all acromegalic patients. The frequency of surveillance depends on the findings. The colon of the acromegalic patient is classically a "megadolichocolon", which requires more careful colonic preparation for colonoscopy by a trained physician with a long colonoscope. The quality criteria for performing colonoscopy must be checked. In addition, a microbial overgrowth syndrome could contribute to more frequent digestive symptoms in acromegalic patients: meteorism, flatulence, nausea, and abdominal pain.

The main side effects of medical treatment of acromegaly are digestive. Hepatic cytolysis often occurs under pegvisomant, with transient transaminase elevation; this is rarely greater than 3 times normal, in which case discontinuation should be discussed. Regular transaminase monitoring is recommended under pegvisomant. Vesicular sludge and/or gallstones is a frequent complication of SRLs, but is mostly asymptomatic and rarely requires surgery. Therefore, ultrasound screening for vesicular complications is not recommended in the absence of symptoms. Digestive side effects under SRLs are very frequent (diarrhea, abdominal pain, nausea and abdominal distension), usually of moderate intensity, and seem to decrease with over time of treatment. They are possibly secondary to the functional pancreatic insufficiency induced by SRLs, and could be reduced by pancreatic extracts [13,34,38,80,89,106–110].

5.8. Metabolic complications

Abnormalities of carbohydrate metabolism are very common in acromegaly, in more than 50% of patients, and are linked to insulin resistance secondary to chronic hypersecretion of GH. Diabetes is present in 20–35% of acromegalic patients. Thus, screening for diabetes should be systematic, by measuring fasting blood glucose and HbA1c and even performing OGTT if necessary. Abnormalities of carbohydrate metabolism regress when acromegaly is controlled. However, acromegaly-related diabetes may sometimes require its own treatment. Furthermore, pasireotide, a somatostatinergic agent sometimes used in the treatment of acromegaly, may cause diabetes and requires close monitoring of blood glucose levels, particularly during the first 3 months of treatment. Acromegaly can also cause lipid abnormalities, mainly hypertriglyceridemia and a decrease in HDL-cholesterol. Finally, metabolic steatosis is common, in > 60% of acromegalic patients [3,39,77,111–114].

5.9. Neoplastic complications

The prevalence of cancer in acromegalic patients is close to 11%, significantly higher than in the general population [89,115–117].

The estimated prevalence of colon cancer in the acromegalic population is 0.9–2.4%.

An initial colonoscopic examination is suggested for all patients over the age of 40 years when acromegaly is diagnosed. In younger patients, individual susceptibility factors to colon cancer should be taken into account. Follow-up includes: (1) colonoscopy at 3 years, if elevated IGF-I and polyps are diagnosed at first colonoscopy; (2) colonoscopy at 5 years, if no polyps are seen at initial examination but IGF-I is uncontrolled, or if $\geq$ 2 polyps are seen at initial examination but IGF-I is normal. Follow-up is comparable to that in the general population in case of normal IGF-I and absence of polyps at initial diagnosis [4,80,89,107,116,118].

Thyroid cancer is one of the most common cancers encountered in acromegaly, although higher prevalence compared to the gen-

eral population is controversial. Thyroid monitoring in acromegalic patients is based on:

- annual thyroid palpation and TSH measurement;
- in the absence of clinical abnormalities, cervical ultrasound at diagnosis of acromegaly and then every 5 years;
- fine needle aspiration biopsy, according to the usual criteria (nodule size and EU-TIRADS classification) [4,80,89,116,119,120].

The increased risk of breast cancer appears to be slight in acromegalic patients. Breast cancer screening is similar to that recommended for the general population, with annual breast palpation as soon as acromegaly is diagnosed, and systematic mammography from the age of 50, or earlier if there are risk factors for breast cancer, in which case mammography every 2 years is recommended [89,116,121].

For urinary tract and prostate cancers, screening and follow-up is the same as in the general population. However, special attention should be paid to ensure that these patients actually undergo the screening offered in the general population. The slightest clinical symptomatology and/or presence of risk factors (smoking in particular) should lead to closer screening [116,121,122].

5.10. Psychological and social complications

The impact of the disease and treatment on self-image and self-esteem, social relationships, schooling or occupational activity and more broadly on quality of life must be assessed.

Psychological care may be necessary at different stages of the treatment process: at the time of the announcement, at treatment initiation, and during the follow-up, or in case of multiple pituitary deficits following surgery. In the adolescent period, early psychological support is important for the young patient and family [99,123–125]. Acromegaly, even in remission, can have repercussions on schooling and/or working life. Depending on the needs (educational assistance, reorganization of schooling and/or financial support, occupational reclassification or invalidity), the patient may be referred to a social worker or the ad hoc structure (local disabled persons' homes: "*Maisons départementales pour les personnes handicapées*" [MDPH]) [126].

6. Special situations

6.1. Genetic forms

Acromegaly related to a genetic predisposition syndrome occurs at a younger age than sporadic acromegaly, and is usually diagnosed after other manifestations of the genetic disease in the case of MEN1 or CNC. Acromegalogigantism may be observed as part of the XLAG syndrome [23].

Pituitary surgery is the first treatment to be discussed in acromegaly with a genetic cause, but must take account of the patient's history and the comorbidities already present in relation to the patient's predisposition syndrome and previous medical history.

The frequent invasiveness in MEN1 patients and those with *AIP* mutations may, depending on tumor volume and visual risk, lead to a discussion of medical treatment as a first-line option. In Carney's complex, the delicate interpretation of somatotroph hyperplasia or multiple adenomas on MRI should be taken into account as a factor that may limit surgical success.

As first-line treatment or after failed surgery, medical treatment with SRLs is discussed, bearing in mind that SRL resistance is more frequent in patients with *AIP* mutation, and that response to pasireotide has been reported to be better in isolated cases. GH antagonists (pegvisomant) are discussed on the same basis as in sporadic acromegaly, although here too poorer response than in sporadic adenomas was observed in some *AIP* mutated patients. Temozolomide may be proposed in some cases of aggressive adenoma. Radiotherapy is discussed after surgery and failure of medical treatment, especially if the pituitary tumor is aggressive.

In patients with McCune-Albright syndrome, acromegaly is usually associated with fibrous dysplasia of the skull base, which complicates the surgical approach; medical treatment is thus to be preferred, even if these patients respond less well to SRLs, often requiring the use of pegvisomant.

Long-term follow-up of genetic acromegaly is important because of the poorer therapeutic outcome and the possibility of another pituitary tumor occurring in this condition [20,22,127–131].

6.2. Agressive somatotroph tumor and carcinoma

Aggressive pituitary tumors are invasive progressive lesions with multiple recurrence and clinically significant tumor growth despite optimal use of standard therapeutic tools (surgery, well-conducted medical treatment and radiotherapy). Most show abnormal proliferation markers: Ki67 $\geqq$ 3% and/or > 2 mitoses per 10 fields and/or > 10 P53 positive nuclei per 10 fields. The prevalence of aggressive somatotroph tumors is low, at < 10% of aggressive pituitary tumors [24,132].

Diagnosis of pituitary carcinoma is based on presence of cerebrospinal or systemic metastases. Pituitary carcinoma is rare, at 0.2% of pituitary tumors, and somatotroph carcinoma is exceptional (5–10% of pituitary carcinomas). Metastasis should be screened for in case of suggestive symptoms or discrepancies between the biological progression and absence of tumor progression. Metastasis screening is based on functional imaging (PET with ^{18}FDG or ^{68}Ga-DOTATATE) and conventional imaging (brain and spinal cord MRI). Diagnosis must be proven histologically [132,133].

The first-line treatment for pituitary carcinoma is temozolomide, an alkylating agent that can be used either as monotherapy (150–200 mg/m^2 daily for 5 days, repeated every 28 days) or in combination with radiotherapy (Stupp protocol) only if the patient has not already been treated with a cumulative dose of radiotherapy considered toxic, 6 weeks of fractionated radiotherapy in parallel with daily temozolomide 75 mg/m^2, preceding the classic temozolomide regimen described above.

If temozolomide is ineffective, options are limited and based on isolated case reports. The most promising are anti-VEGF (bevacizumab), immunotherapy (anti-PD1 with or without anti-CTLA4) and internal vectorized radiotherapy based on labelled ligands of somatostatin receptors [132–135].

The management of these patients must be discussed in a dedicated national multidisciplinary staff meeting and carried out in expert pituitary reference centers (HYPO).

6.3. Pregnancy

The fertility of acromegalic women is lower than in the general population. However, pregnancies have been reported even when acromegaly was not controlled.

Gonadotroph disorders have 4 main origins: (1) hyperprolactinemia related to the presence of a mixed GH/PRL adenoma; (2) disconnection hyperprolactinemia related to the size of the adenoma; (3) gonadotroph insufficiency related to a destruction of gonadotroph cells by mass effect and/or an anti-gonadotroph effect of GH hypersecretion; and (4) more rarely, a direct impact of GH/IGF-I on the ovaries, inducing polycystic ovary syndrome. Anovulation is mainly related to hyperprolactinemia.

It is advisable to plan pregnancy in an acromegalic patient, as it is recommended to stop treatment with SRLs or pegvisomant, if possible 2 months before the start of pregnancy. Dopamine agonist treatment can be continued if necessary.

During pregnancy, a few cases of somatotroph adenoma enlargement have been reported. GH and/or IGF-I measurements are not recommended in pregnancy monitoring. MRI is not necessary unless there is severe headache and/or worsening of the visual field. In case of macroadenoma, visual field examination should be performed at least every trimester. Systematic screening for gestational diabetes is recommended in the first trimester.

Acromegaly is very rarely diagnosed during pregnancy, most often in case of visual field amputation or headache. Treatment with a dopamine agonist should be considered in first line. Data are sparse concerning the fertility of acromegalic men. A recent study suggested that sperm quality is similar to that of the healthy male population, even in the presence of low testosterone levels [8,13,136–139].

7. Pediatric specificities in acromegaly

7.1. Diagnostic features

Growth hormone excess in a growing child is rare. It induces gigantism, with linear acceleration of the statural growth, body mass index and macrocephaly. Other clinical signs are less marked than in adults. Bone age is normal or advanced compared to chronological age.

Biological diagnostic criteria are identical to those used for adults. IGF1 measurement is consistently greater than +2 SDS but interpretation of IGF1 should be based on standardized values for sex, age and pubertal stage. OGTT may be misinterpreted in tall adolescents. Hyperprolactinemia is often associated.

The appearance on MRI is often an invasive pituitary macroadenoma, but a hypothalamic origin by hypersecretion of GHRH is possible in the context of neurofibromatosis type 1 (NF1) with optic glioma or gangliocytoma [6,7,9,17,140,141].

7.2. Etiological features

More often than in adults, acromegalic gigantism is part of a familial or syndromic form with identification of a genetic abnormality: multiple endocrine neoplasia (*MEN1* or *MEN4*), familial isolated pituitary adenoma syndrome (FIPA), Carney complex, McCune-Albright syndrome, or X-linked acrogigantism (X-LAG). These forms occur at a younger age, with higher growth hormone levels, larger and more invasive tumors, poorer response to medical treatment and more frequent failure of surgical treatment [7,17,128,142,143].

Genetic panel analysis (next-generation sequencing) or even in the exome or genome should be proposed systematically if acromegaly is diagnosed during infancy or adolescence.

7.3. Therapeutic features

Choice of treatment is on a case-by-case basis, within the framework of a national multidisciplinary meeting of the pituitary reference centers.

In the absence of specific pediatric studies, the biological therapeutic objectives are identical to those for adults: IGF1 normalized for sex, age and pubertal stage and random GH < 1 μg/L or < 0.4 μg/L after OGTT.

Additional treatment goals in adulthood are to limit adult height and monitor pubertal development [13,17,28].

Surgery is the first-line treatment, most commonly by transphenoid approach. Strategy is discussed in case of suprasellar extension, where a transcranial approach may be necessary, and in case of invasive macroadenoma or global pituitary hyperplasia, where first-line drug treatment may be advised. Neurosurgery should only be performed by an experienced neurosurgical team.

Drug treatment is considered in second line if tumor removal is incomplete or in first line in case of invasive macroadenoma or pituitary hyperplasia. Cabergoline has often little effect on GH secretion, and acts mainly on prolactin secretion. SRLs have limited efficacy in children, with resistance in 70% of cases. Pegvisomant is indicated alone or in combination with SRLs in case of SRL resistance. Reported cases are rare, but efficacy is consistent. There is a risk that the tumor may increase in size under such treatment, requiring regular radiological monitoring of tumor size in a specialist center. Radiotherapy in pediatric management is limited to rare therapeutic impasses, which are discussed in the national multidisciplinary meetings of the pituitary reference center. Additional treatment with sex steroids may be discussed, to accelerate fusion of the growth plate and limit final height [17,28,60,140,142–144].

7.4. Child/adult transition

Acromegaly managed at the child/adult transition is most often secondary to macroadenoma. Follow-up is essential for continued active management of acromegaly, treatment of pituitary deficits and management of comorbidities.

The circumstances and criteria for biological diagnosis in adolescence are the same as in childhood, but with higher physiological IGF-I thresholds.

The choice of treatment (medical or surgical) must be made on a case-by-case basis according to the hormonal and tumoral evolution of the acromegaly, taking into consideration the risks of damage to other pituitary functions, and particularly gonadotroph function. The therapeutic objectives for a patient treated during the transition period should not differ from the recommended objectives: i.e., normalization of IGF-I and GH. However, growth monitoring is parameter in this context, especially to assess treatment effect. In addition, the management of acromegaly at transition raises the common issue of the management of associated pituitary deficits. It is important to continue replacement therapy, with reassessment and adaptation to the specific needs of this period. The transition period should be an opportunity to review the syndromic and genetic etiology of acromegaly and monitoring by multidisciplinary teams from expert centers [13,17,28,145,146].

Global personalized management of young patients must be based on discussion, taking into account their emotions, adapting to their priorities and lifestyle, setting up specialized places involving the adolescent and the pediatric and adult endocrinologists. During transition, the young person must be able to understand and explain his or her disease and treatment, the importance of long-term follow-up, and the possibility of syndromic disease; these elements are important to guarantee compliance with follow-up and treatment in adulthood, and to avoid breaks in follow-up and the medical consequences that they could cause [66,146,147].

Patient association network

As soon as the disease is diagnosed, health professionals are prompted to inform patients of the existence of patient associations. In France, in 2015, the patient association "Acromégales, Pas Seulement. . ." (APS) was created in order to contribute to a better management of acromegalic patients (https://www.acromegalie-asso.org/).

Disclosure of interest

Conflicts of interest of each author are available on the following reference center's website HYPO (http://fr.ap-hm.fr/sites/default/files/files/defhy/PNDS-Acromegalie-DPI-combinees.pdf).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ando.2023.08.003.

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