In The Name Of GOD

Update on Acromegaly;
Diagnosis, Remission and Treatment
What's new?!

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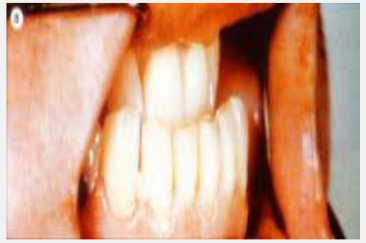
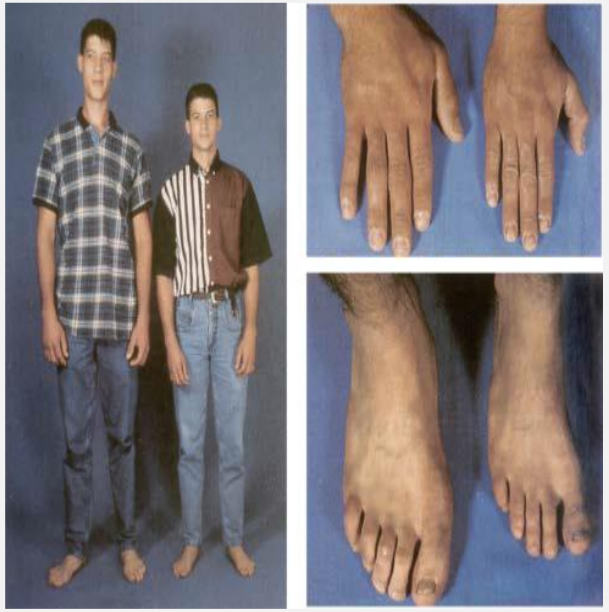
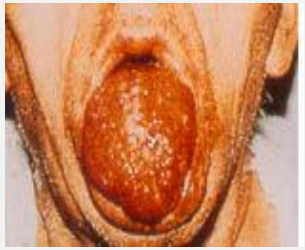
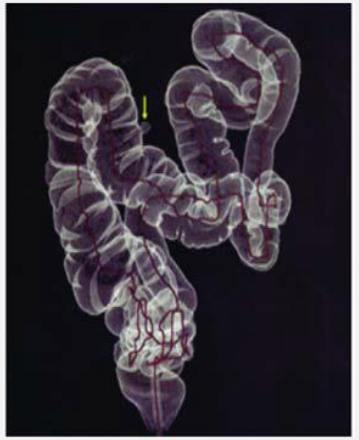
Agenda

- Introduction
- Who should we screen for acromegaly?
- When should be offered genetic testing?
- What is the most appropriate lab workup?
- How to treat a patient who is not in remission after surgery?
- Can a personalized approach be considered for each patient?

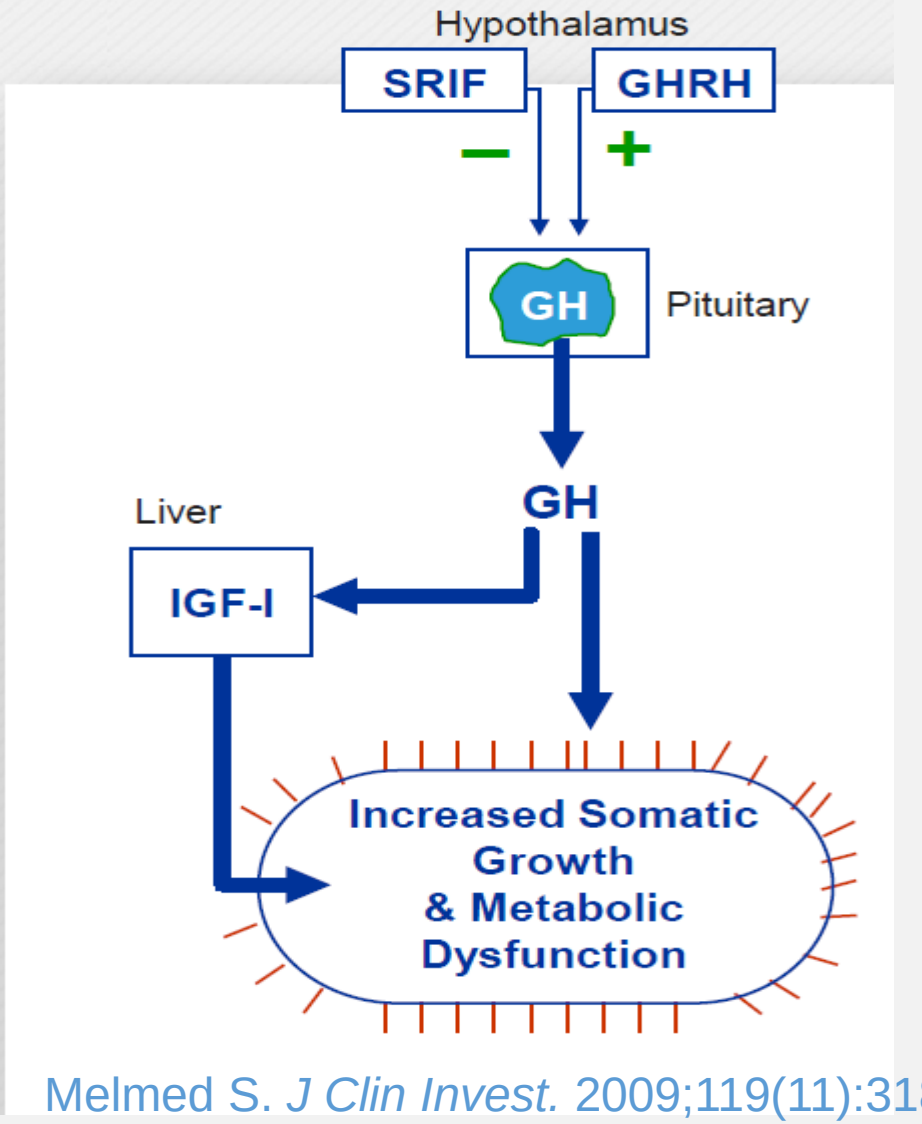








GH-Secreting Adenoma: Persistent GH and IGF-1 Excess



Chronic GH excess, from *pituitary adenoma*

Advanced disease at diagnosis due to long delays and impact of chronic GH/IGF-1 exposure.

Comorbidities and high mortality if chronically uncontrolled.

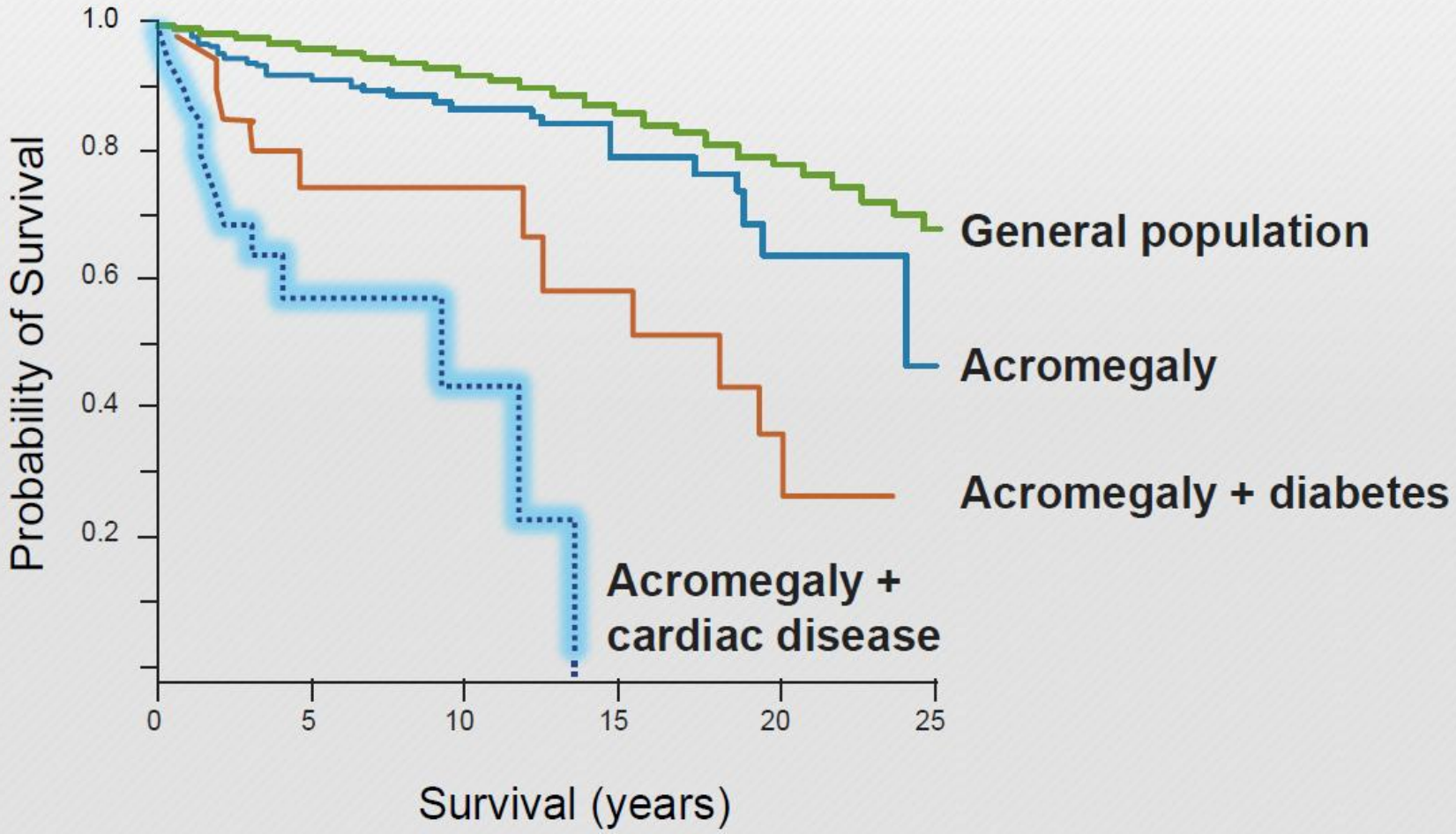
Melmed S. *J Clin Invest.* 2009;119(11):3189- 202.

Introduction

- **Incidence** :slightly higher in **females**.
- **Men: younger** at diagnosis, by a median of 4.5 years.
- **Women** may show both increased incidence and mortality risk.
- **Younger** patients tend to have larger and more aggressive tumors that are diagnosed earlier.
- **Older** patients usually have smaller and less aggressive tumors.

Andrea Giustina,Consensus on criteria for acromegaly diagnosis and remission,2024

Acromegaly Life Expectancy ⬇ 10 years



Adapted from Raja soorya C, et al. *Clin Endocrinol.*1994;41(1):95-102.

CASE:

49-Year-Old woman

Acral enlargement

Increased interdental spaces

Excess sweating

Jaw prognathism

Headache

HTN, Pre DM

IGF-1:1256 ng/mL (123-256)

Prl: 12 ng/mL

Normal cortisol, ACTH, TSH, T4

What would you suggest next in this setting?

A. Repeat IGF1
B. OGTT
C. Basal GH
D. Pituitary MRI

Evaluation at Diagnosis

Complication	Screening at Diagnosis
Cardiovascular	• Ambulatorial BP
	• 24-h monitoring of BP[a]
	• ECHO
	• Electrocardiogram (if cardiac rhythm abnormality at physical examination)
	• Symptoms: referral to cardiologist
Respiratory	• Epworth scale
	• Polysomnography (if symptoms?)
Bone	• Thoracic and lumbar x-ray or VFA
Articular	• Clinical evaluation
Cancer	• Colonoscopy (especially if >40 y)
	• Thyroid US (only if palpable nodule)
Metabolic	• Glucose levels and lipid profile
Endocrine	• Pituitary function
QoL	• AcroQol (repeat yearly)

Modified from Gadelha MR, et al. *Endocr Rev.* 2019;40(1):268-332.

Which Clinical Features and Conditions Should Raise *Suspicion* Acromegaly?

- In typical clinical manifestations, particularly those with acral and facial features of acromegaly.
- **Several** acromegaly-related conditions:

  SAS , debilitating arthritis, CTS, DM , HTN, colon polyps,

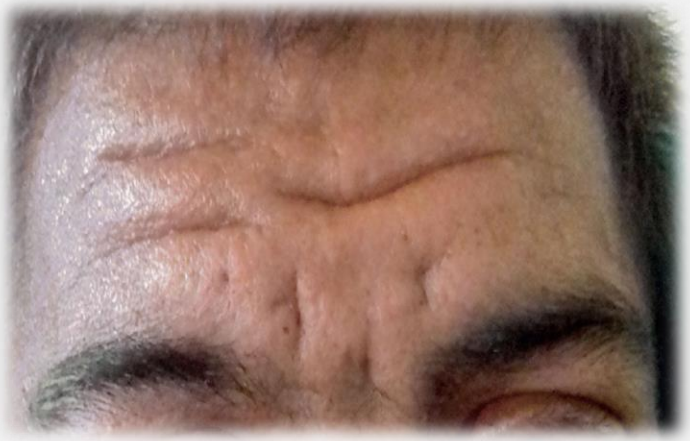
  or cancer.
- A pituitary mass, even if typical acromegaly manifestations are absent.

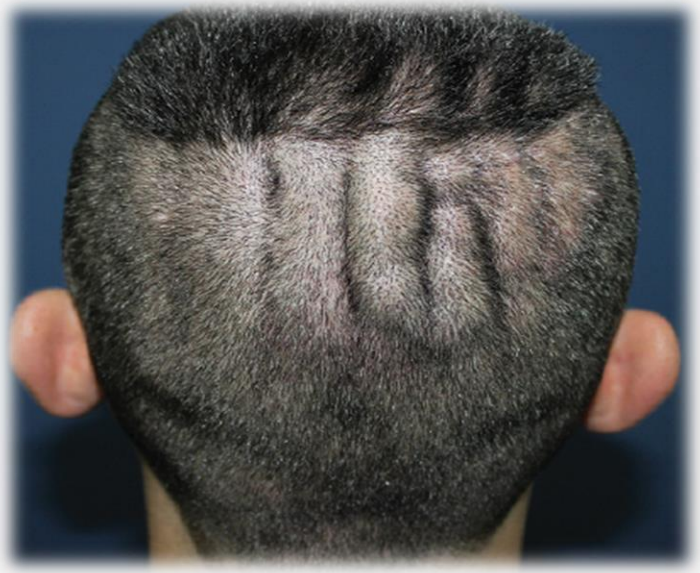
Diagnosis and Management of Acromegaly:
A Consensus Statement of the Pituitary Study Group of the
Portuguese Society of Endocrinology, Diabetes and Metabolism,2025
Endocrinology Insights,2025

Which Clinical Features and Conditions Should Raise Suspicion for Acromegaly?

- Accelerated linear growth or tall stature, particularly if ≥2 SD above the mid parental height, and typical clinical features of acromegaly and/or acromegaly-related conditions or comorbidities coexist.

- Presenting with atypical features, specifically ***hyperhidrosis, pachydermia, and cutis verticis gyrata.***





Diagnosis and Management of Acromegaly:
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When should genetic testing be offered and which genes should be tested?

For AIP and MEN1 mutations

(except if MEN1 syndromic features exist in the patient or any family member), and in the following situations:

1. FH of pituitary tumors (of **any type**)
2. **Micro** or **macro**adenomas with onset at age ≤18 years (including all cases of pituitary gigantism)
3. **Macro**adenomas with disease onset at age ≤30 years.
4. Double or multiple GH-secreting pituitary tumors may be considered for genetic testing, commencing with testing for AIP, if syndromic features are absent, followed by MEN1.

What Is The Most Appropriate Laboratory Workup?

In 2014, guidelines from the Endocrine Society :

They recommended using IGF-I normalized to **age** but not sex for the diagnosis.

Confirmed by lack of suppression of GH < 1 µg/L during OGTT if necessary,

Therapeutic goal:

age-normalized IGF-I and random GH < 1.0 µg/L.

Andrea Giustina,Consensus on criteria for acromegaly diagnosis and remission, 2024

What Is the Most Appropriate Laboratory Workup?

Variability in IGF-1 assays across **different laboratories** may pose further challenges.

A multi centric UK-based study that found more than a twofold difference in IGF-1 levels in the same sample among different laboratories, leading to diagnostic failure of acromegaly in 30% of the centres.

To overcome such variability serum IGF-1 should be assayed in the same laboratory for serial follow-up.

Pokrajac A, Variation in GH and IGF-I assays limits the applicability of international consensus criteria to local practice.
Clin Endocrinol. 2007;67(1):65–70.

What Is The Most Appropriate Laboratory Workup?

IGF-1 levels can be **blunted** in patients who exhibit resistance to GH action related to:

- Advanced liver or kidney disease
- Severe hypothyroidism
- Malnutrition
- Anorexia
- Poorly controlled DM
- Women receiving oral Estrogens

Diagnosis and Management of Acromegaly:
A Consensus Statement of the Pituitary Study Group of the Portuguese Society of Endocrinology
Diabetes and Metabolism, Endocrinology Insights, 2025

What Is The Most Appropriate Laboratory Workup?

Following on studies underscoring the challenges of uniformly applying results of GH and IGF-I assays in the clinic the 14th Acromegaly Consensus Conference held in 2022 in Italy, once again ***revisited the question of how to define biochemical criteria for acromegaly diagnosis and evaluation of therapeutic efficacy.***

Recent consensus:

In patients with typical signs and symptoms of acromegaly:

IGF-1 levels >1.3 times the ULN for age **confirm** the diagnosis

without the need for further testing .

In patients with equivocal results:

Repeat the IGF-1 measurement.

OGTT, may also be useful.

Normal subjects will exhibit suppression of GH to undetectable levels.

Diagnosis and Management of Acromegaly:
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Endocrine Society guidelines, (2014)

Cut-off of GH <1.0 µg/L (within 2 h after oGTT)

(usually excludes)

GH nadir <0.4 µg/L may be more reliable in establishing or ruling out acromegaly

According to the latest acromegaly consensus:

If an OGTT is performed (fasting state) :

GH levels assessed after 30, 60, 90, and 120 min.

The lack of suppression GH nadir level :

- ✓ **<0.4 µg/L for BMI <25 kg/m2**
- ✓ **<0.2 µg/L for BMI ≥25 kg/m2**

Healthy premenopausal women on OCP typically have higher GH levels recommended to discontinue these drugs 4 weeks prior to Test.

GH may fail to suppress in healthy adults!

should be interpreted cautiously, according to the individual **physiological, pharmacological, pathological, and clinical factors**.

❖GH may fail to suppress in healthy adults, such as:

✓ Adolescents

✓ Young females (particularly those on Estrogen-ocp)

✓ liver or kidney disease

✓Poorly controlled DM

✓ Anorexia

Diagnosis and Management of Acromegaly:
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One-third of patients may show a paradoxical increase in GH after OGTT.

In DM2, the OGTT appears to be safe and effective for the diagnosis.

(Due to the ***suppressive*** Effect of hyperglycemia on GH), the results should be interpreted with caution, particularly in patients with uncontrolled DM.

Diagnosis and Management of Acromegaly:
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In most cases, diagnosis is clear without a need for OGTT .

Interpretative difficulties of OGTT outweigh the potential advantages.

The consensus recommend

This test be reserved for patients in whom

baseline hormone levels do not clarify the diagnosis.

Andrea Giustina, Consensus on criteria for acromegaly diagnosis and remission 2024

48-Year-Old woman

Acral enlargement

Increased interdental spaces

Excess sweating

Jaw prognathism

Headache

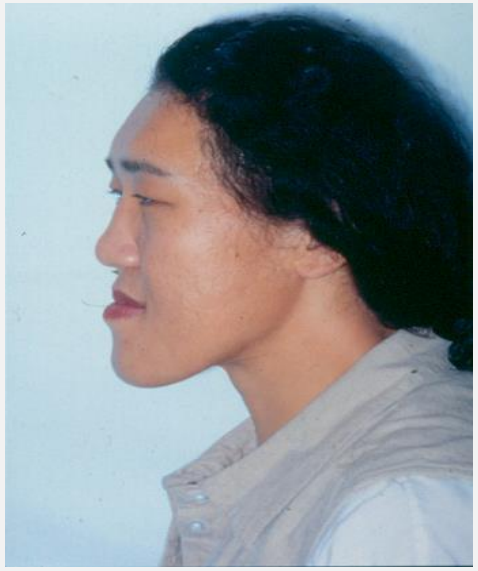
HTN, Pre DM

IGF-1: 1256 ng/mL (123-256)

Prl :12 ng/mL

Normal cortisol, ACTH,

TSH, T4



What would you suggest next in this setting?

A. Repeat IGF1

B. OGTT

C. Basal GH

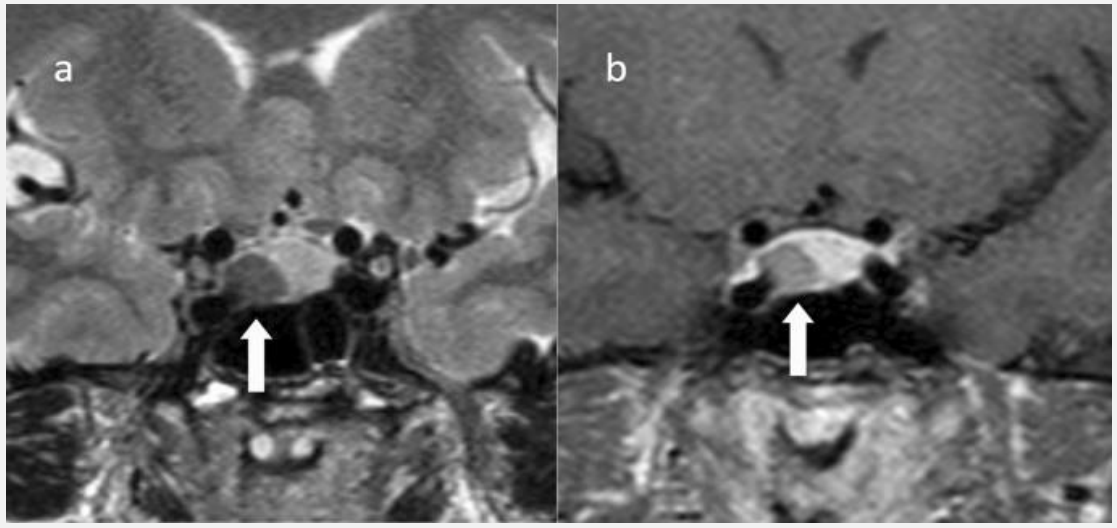
D. Pituitary MRI

Imaging Modality?

- Using 1.5 Tesla or 3 Tesla scanners.
- with **two**-millimeter slices, to identify small **micro**adenomas.

✓T2-weighted MRI **signal intensity** : predict the response to SRLs.

✓Hypo intense : better response to SRLs.



Functional imaging?

Detecting small microadenomas

Sites of residual disease that may be amenable for repeat surgery.

❖11Cmethionine:

Useful when MRI results are **indeterminate** or

when the true **extent of lateral tumour** extension is **unclear.**

❖68 Ga-DOTA-somatostatin analogue.

Not have a detectable tumor (**ectopic disease**) such as **Thoracic and abdominal** CT scan.

❖PET/CT 18-DG-PET :

Ectopic **malignant tumors.**

Diagnosis and Management of Acromegaly:
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Case

Her MRI report is as follows:

2.0 x 1.4 cm adenoma with left cavernous sinus extension.

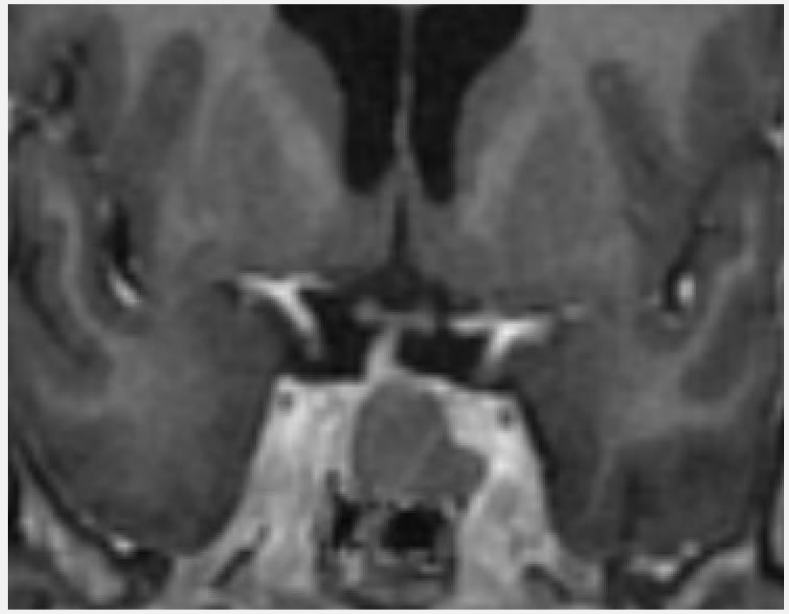
Surgery is performed.

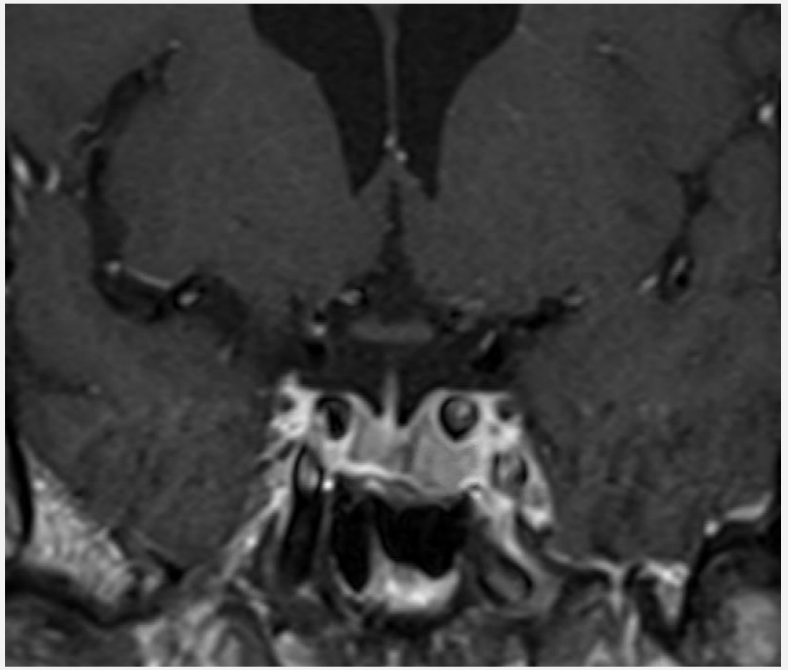
❖ lab changes **3 mouth** post operation are as follows:

IGF-1: 894 ng/mL (123-256)

Next step?

A. Start octreotide or lanreotide
B. Start pasireotide
C. Start cabergoline
D. Reoperation





Preoperative Medical Treatment?

Preoperative treatment with SRLs administered 3–6 months before surgery?

✓severe acromegaly comorbidities and high surgical risk.

(severe pharyngeal thickening and SAS, high output HF)

✓Expert neurosurgeon is not available.

✓ When surgery is expected to be significantly delayed.

✓Refuse pituitary surgery.

✓Tumors with **Cavernous sinus invasion** without chiasmal compression, when significant **debulking is not feasible**.

An immediate postoperative GH!

For biochemical monitoring during or after treatment?

IGF-1 correlates with improvement in symptoms and signs.

GH is more indicative of tumor secretory activity.

Postoperative:

Random GH levels

GH nadir during an OGTT

Long-term remission.

GH level <1.0 µg/L (day 1–14)

highly predictive of biochemical remission.

and a GH nadir level <0.4 ng/mL 1 week postoperatively showed a PPV >95% for surgical remission.

Tyler Cardinal, Postoperative GH and Degree of Reduction in IGF-1 Predicts Postoperative Hormonal Remission in Acromegaly

Biochemical monitoring during or after treatment?

- The postoperative decline of IGF-1 is slower than that of GH likely due to the longer half-life of **IGFBPs**.
- IGF-1 in the early postoperative are highly variable.
- Stabilize 12 weeks after surgery.

  should be measured at **least 12 weeks postoperatively** to determine the biochemical status of the disease .
- If preoperative SRLs were used: IGF-1 should be repeated at 3–6 months to confirm remission, since the SRLs carryover effect may influence postoperative IGF-1 levels.

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Remission or Cure?

Term “remission” should be used preferentially instead of “cure”.

Normal IGF-1 levels adjusted for **age** should be the main criteria to define remission.

In the cases of **borderline** IGF-1 levels:

A random GH <1.0 µg/L

Or

GH nadir < 0.4 µg/L after OGTT with an ultrasensitive GH assay may be useful in defining remission.

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Endocrinology Insights, 2025

Criteria for remission

- Maintaining serum IGF-I level in the **mid to upper half** of the age-related reference range could be considered in clinically controlled patients to avoid induction of **GH deficiency**.

  Although biochemical remission is the primary assessment of treatment outcome, it is not the only goal of treatment in acromegaly.

- In all cases, biochemical findings should be interpreted within the ***clinical context*** of acromegaly signs and symptoms.

Andrea Giustina,Consensus on criteria for acromegaly diagnosis and remission 2024

Clinical Assessments

SAGIT and ***ACRODAT*** (Acromegaly Disease Activity Tool) are scoring tools that use multiple disease-specific parameters to ***define severity of Acromegaly***.

Both instruments may be useful in for assessing changes in disease severity and progression over time.

(b)

S	SIGNS & SYMPTOMS	**Which of the symptoms (S) from the list below is your patient experiencing?**	**Score S**	**Score S** *from 0 to 4 (0 = no Signs & Symptoms ticked)*
		Headache ☐ Sweating ☐ Joint symptoms ☐ Swelling ☐	Sum up the number of symptoms (S) ticked	S = _____
A	ASSOCIATED COMORBIDITIES	**Which of the associated comorbidities (A) from the list below is your patient experiencing?**	**Score A**	**Score A** *from 0 to 6 (0 = no Comorbidities ticked)*
		Altered carbohydrate metabolism ☐ Hypertension ☐ Sleep apnea ☐ Heart disease ☐ Hypopituitarism ☐ Active malignant tumor ☐	Sum up the number of comorbidities (A) ticked	A = _____
G	GH NADIR WITH OGTT	**Report concentration result of GH nadir with OGTT**	**Corresponding score**	**Score G** *from 0 to 4*
		≤ 0.4 µg/l ○ > 0.4 to < 1.0 µg/l ○ ≥ 1.0 to < 2.5 µg/l ○ ≥ 2.5 to < 5 µg/l ○ ≥ 5 µg/l ○	G = 0 G = 1 G = 2 G = 3 G = 4	G = _____
	OR	OR	OR	OR
	GH RANDOM OR MEAN CONCENTRATION OF GH SERIES	**Report concentration result from the test (GH random or mean concentration of GH series)**	**Corresponding score**	**Score G** *from 0 to 4*
		≤ 1.0 µg/l ○ > 1.0 to < 2.5 µg/l ○ ≥ 2.5 to < 5 µg/l ○ ≥ 5 to < 10 µg/l ○ ≥ 10 µg/l ○	G = 0 G = 1 G = 2 G = 3 G = 4	G = _____
I	IGF-I	**Report level relative to age-adjusted upper limit of normal** *(ULN)*	**Corresponding score**	**Score I** *from 0 to 3*
		Normal ○ < 1.3 ULN ○ ≥ 1.3 to < 2 ULN ○ ≥ 2 ULN ○	I = 0 I = 1 I = 2 I = 3	I = _____
T	TUMOR	**Describe the tumor** *(tick the worst choice by default)*	**Corresponding score**	**Score T** *from 0 to 5*
		No visible tumor ○ Micro tumor intrasellar < 10 mm ○ Macro tumor intrasellar ≥ 10 mm ○ Extrasellar tumor < 40 mm ○ Invasive tumor ○ Giant tumor ≥ 40 mm ○	T = 0 T = 1 T = 2 T = 3 T = 4 T = 5	T = _____

✓**If SAGIT-G = 0, 1, or 2 and SAGIT-I = 0:**

91% of patients' treatment remained unchanged.

✓**If SAGIT-G = 0, 1, or 2 and SAGIT-I = 1, 2, or 3:**

71% of patients' treatment also remained unchanged.

✓ **If SAGIT-G = 3 or 4 and SAGIT-A = 0, 1, or 2:**

70% of patients' treatment had to be intensified or initiated.

✓**If SAGIT-G = 3 or 4 and SAGIT-A = 3, 4, or 5:**

100% of patients, treatment had to be intensified or initiated.

How to Treat a Patient Who Is Not in Remission after Surgery?

Medical therapy should be initiated.

- **Somatostatin receptor ligands**

Octreotide

Lanreotide

Pasireotide

- **Dopamine agonists**

Bromocriptine

Cabergoline

- **GH receptor (GHR) antagonists**

Pegvisomant

Katz nelson, et al. *J Clin Endocrinol Metab.* 2014;99(11):3933-51.

First-generation SRLs

- Octreotide LAR and lanreotide Autogel are first-line of medical treatment in **most cases**.
- These drugs are usually administered monthly.
- Target the SST2 expressed.
- Concomitantly anti-secretory and anti-proliferative effects.

*Remission with adenoma-directed **medical therapy***

As injectable SRL is administered monthly, timing of assessment for IGF-I could influence determination of biochemical control.

Recommendation:

- IGF-I level measured in the last week before the next injection.
- Should be used to determine a need for dose titration or consideration of alternative treatment options if normalization is not achieved.

Andrea Giustina, Consensus on criteria for acromegaly diagnosis and remission 2024

Oral octreotide capsules

What's new?!

An evolution in treatment for patients with acromegaly

New formulation of octreotide!

- Oral Octreotide Capsules (OOC)
- Approved by the US FDA, in 2020.
- Effective for patients who have achieved a biochemical response with stable doses of injectable SRLs. (For long-term maintenance treatment)

Currently no data supporting the use of OOC as primary medical therapy in SRL-naïve patients.

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Oral Octreotide Capsules (OOC):
MYCAPSSA
What's new?

- Enteric-coated capsules.
- Each capsule contains 20 mg of octreotide.
- 20 mg OOC has similar pharmacokinetics to SC injection of 0.1 mg of SC octreotide.
- The maximum dose: 80 mg daily
- IGF-I for the purposes of dose titration should be done after at least 2 weeks of treatment .

Orally with a glass of water on an empty stomach, at least 1 hour before a meal or at least 2 hours after a meal.

Oral octreotide absorption in human subjects:
comparable pharmacokinetics to parenteral octreotide and
effective growth hormone suppression. J Clin Endocrinol Metab

Second-generation SRL

- Pasireotide
- Higher affinity for SST4 and SST5 receptor subtypes, some affinity for SST2.
- Effective in patients not controlled with **maximal doses** of octreotide LAR.
- Risk of drug-induced
  - Hyperglycemia ≤ 70%
  - DM ≤40%
- Impaired insulin and incretin secretion.

Should be used in patients with resistance to first-generation SRLs, especially those with normal glucose metabolism and when there is a **concern with tumor mass.**

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Cabergoline:

A modest effect on acromegaly control.

Low baseline IGF-1 levels **predictors** of higher likelihood of biochemical response.

Recommended as first-line medical therapy :

Surgery has failed to achieve biochemical control and IGF-1 levels are only mildly elevated (<1.5 times the ULN)

add-on in cases of partial response to SRLs or pegvisomant.

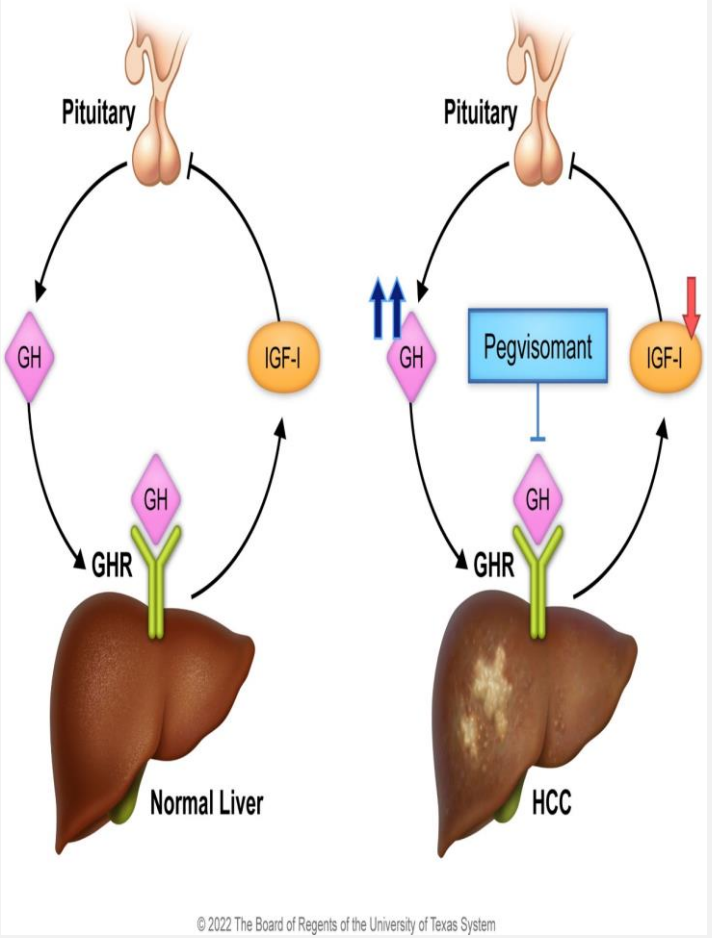
Pegvisomant

- GH analogue with enhanced **affinity for the GH receptor**.
- Preventing the **signaling cascade activated** by GH receptor-binding.
- Second-line medical therapy with intolerance or incomplete biochemical response to maximal doses of SRLs.

It does not target the pituitary tumour.

GH hypersecretion persists during treatment

but tumor growth is rare (i.e., <5%).



In patients with:

large tumors abutting the optic chiasma and other vital structures .

Other tumor-targeted treatments should be preferred.

Pegvisomant is interest for individuals:

DM or glucose intolerance, as it improves glycemic control independently of IGF-1 control.

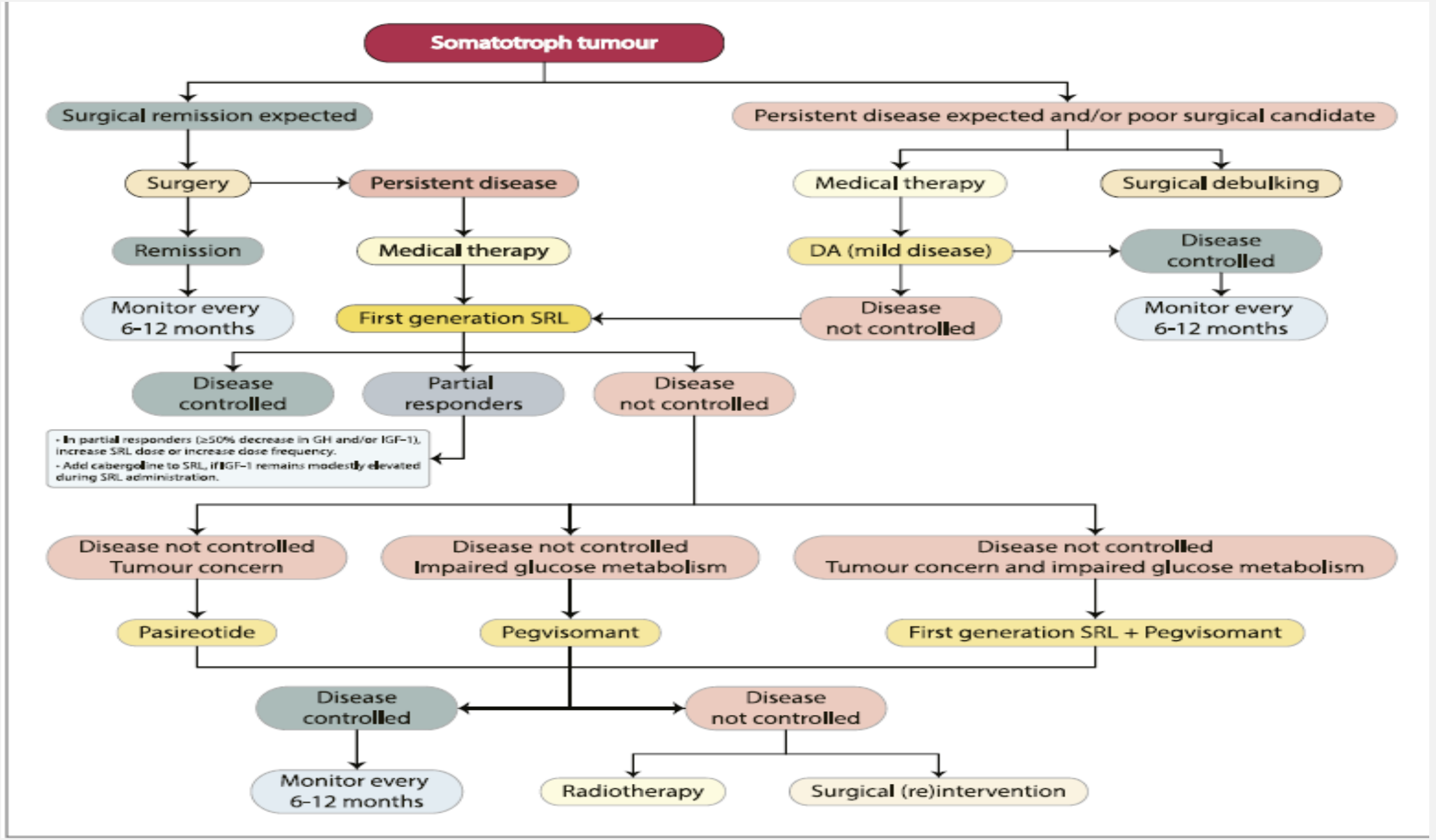
Highly effective in blocking the GH action

Normalizing the IGF-1 levels in **90% of patients in clinical trials.**

✓Tumor growth in ~7% of cases.

✓More frequent during the first year.

✓All were associated with discontinuation of SSA.

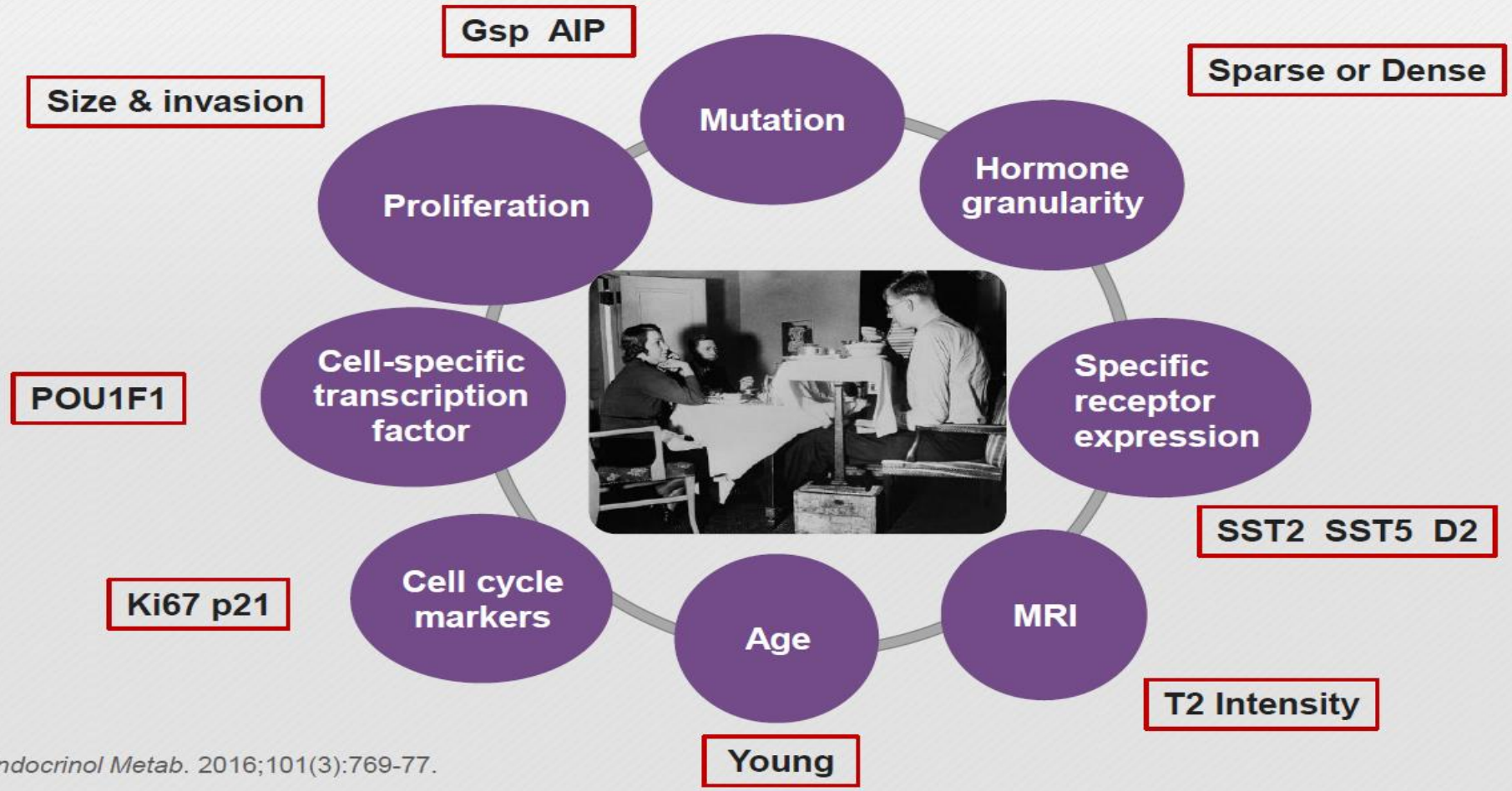

Somatotroph tumour
Surgical remission expected
Persistent disease expected and/or poor surgical candidate
Surgery
Persistent disease
Medical therapy
Surgical debulking
Remission
Medical therapy
DA (mild disease)
Disease controlled
Monitor every 6–12 months
First generation SRL
Disease not controlled
Monitor every 6–12 months
Disease controlled
Partial responders
Disease not controlled
• In partial responders (≥50% decrease in GH and/or IGF–1), increase SRL dose or increase dose frequency.
• Add cabergoline to SRL, if IGF–1 remains modestly elevated during SRL administration.
Disease not controlled Tumour concern
Disease not controlled Impaired glucose metabolism
Disease not controlled Tumour concern and impaired glucose metabolism
Pasireotide
Pegvisomant
First generation SRL + Pegvisomant
Disease controlled
Disease not controlled
Monitor every 6–12 months
Radiotherapy
Surgical (re)intervention

Possible predictors of biochemical response to SRLs:

Higher likelihood of achieving biochemical control:

- ***Older age***
- ***Female sex***
- ***Lower serum IGF-1, and GH levels at baseline***

Can We Personalize Acromegaly Outcomes? !



Melmed S. *J Clin Endocrinol Metab*. 2016;101(3):769-77.

Case

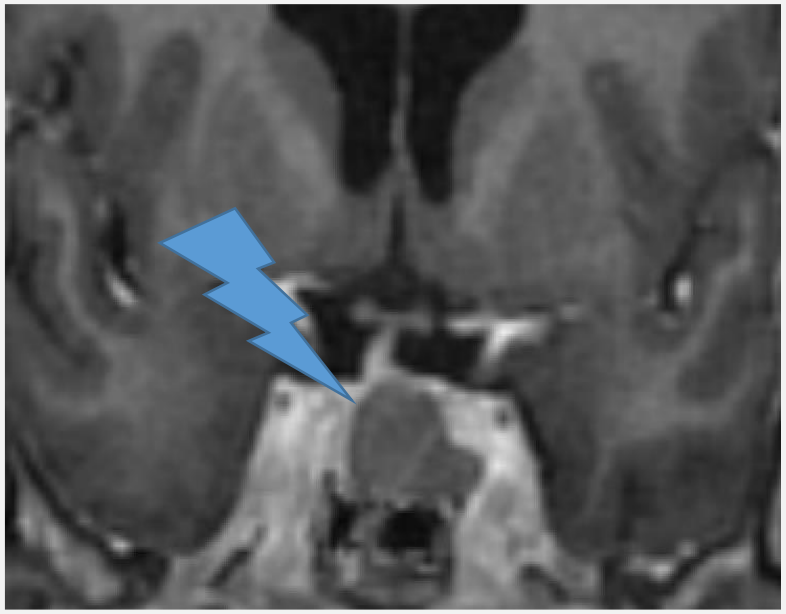
Her MRI report is as follows:

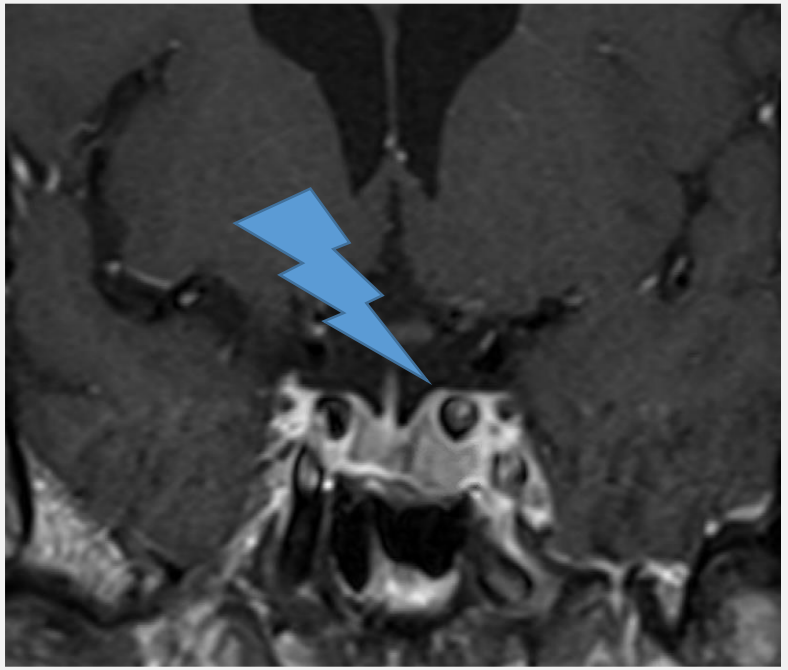
2.0 x 1.4 cm adenoma with left cavernous sinus extension.

Surgery is performed.

- lab changes **3 mouth** post operation are as follows:

  IGF-1: 894 ng/mL (123-256)





Next step?

A. Start octreotide or lanreotide
B. Start pasireotide
C. Start cabergoline
D. Reoperation

For the patient, 20 mg of sandostatin LAR was started monthly.

After 3 months: Headaches improved.

- No longer has snoring.
- Colonoscopy and echocardiogram normal

IGF-1: 378 ng/mL (123-256)

A. Increasing the dose or decreasing intervals
B. Start pasireotide
C. Start cabergoline
D. Start Pegvisomant
E. Reoperation

After 3 month:
IGF1: 245 ng/ml

Take Home Message:

- Typical manifestations are not always necessary to screen for acromegaly, and the presence of a number of atypical manifestations, especially if several occur together, should prompt us to consider screening for this disease.

✓***Typical clinical signs and symptoms:***

IGF-I > 1.3×ULN for age confirms the diagnosis.

For ***equivocal results***, IGF-I can be repeated ***or perform OGTT .***

Take Home Message:

After surgery:

Random GH assessment on day 1–14 predicts remission.

✓IGF-I should be measured at 12 weeks after surgery to determine postoperative remission.

✓OGTT might be helpful in evaluating patients with borderline IGF-I and clinical signs of disease activity .

Take Home Message:

- For patients who have achieved a **complete or partial biochemical** response on injectable SRLs, new formulation of octreotide, oral octreotide, can be used.
- **Pasireotide,** effective in patients **not** controlled with **maximal doses** of First -generation SRLs especially those with **NL glucose metabolism**.
- Cabergoline **monotherapy**, is recommended only for patients with **mild (<1.5 ULN**) elevations of IGF-I levels and symptoms.
- **Pegvisomant** useful for patients are **resistant to SRL**, as well as patients with **hyperglycemia.**
- **IGF1** measurement is the appropriate marker of patient responsiveness.


Thank you