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Acromegaly

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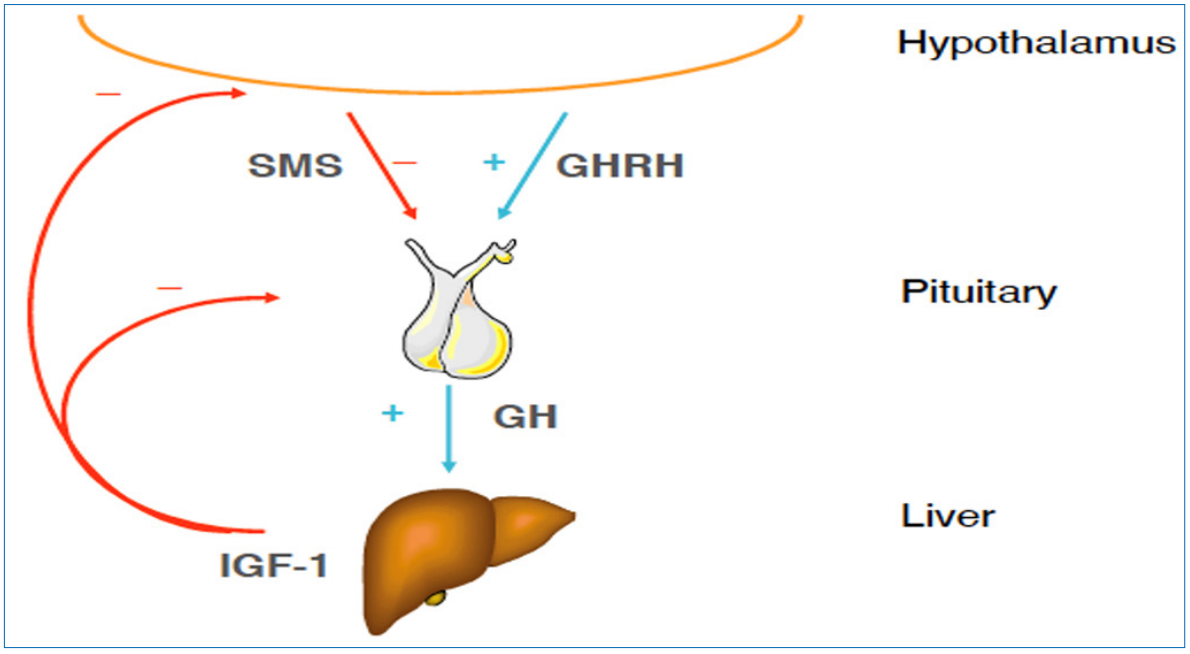
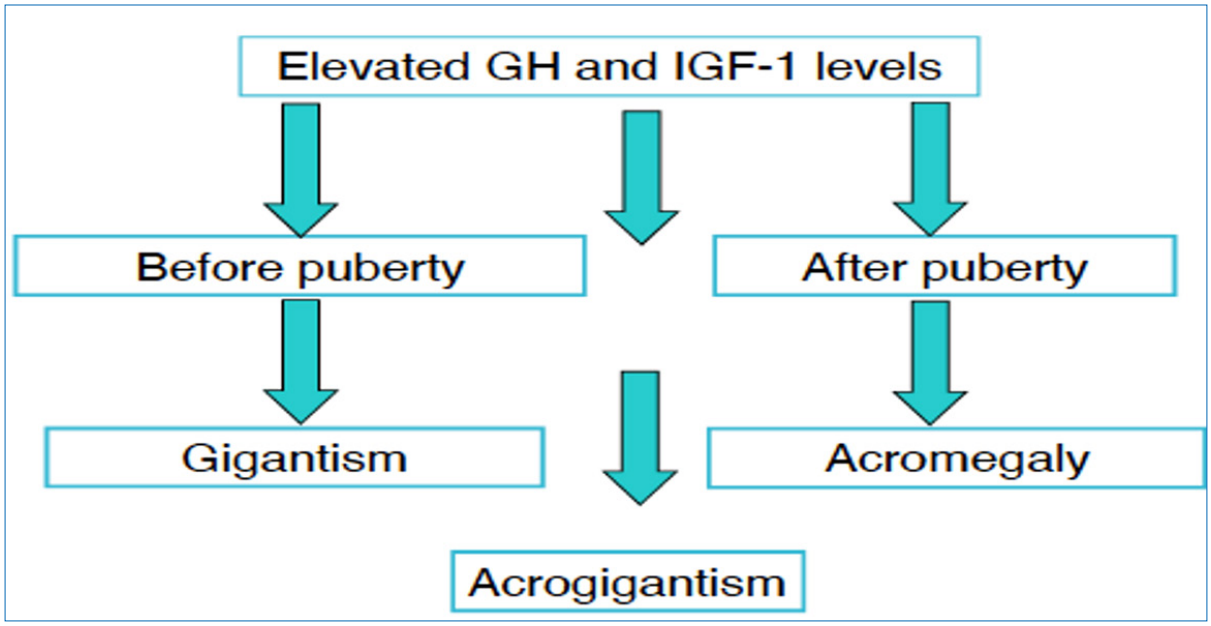
Objectives

1. Clinical presentation
2. Diagnosis of Acromegaly and additional hormonal and metabolic assessment
3. Treatment modalities of Acromegaly
4. Prognosis

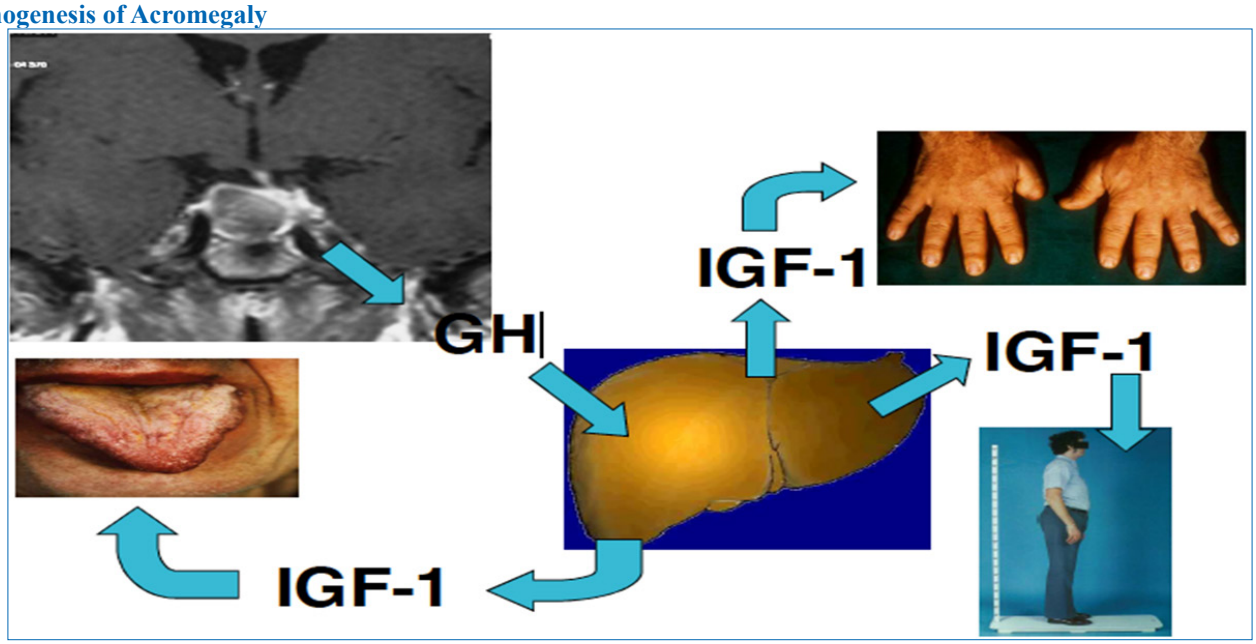
Regulation of GH Secretion



Pathophysiology

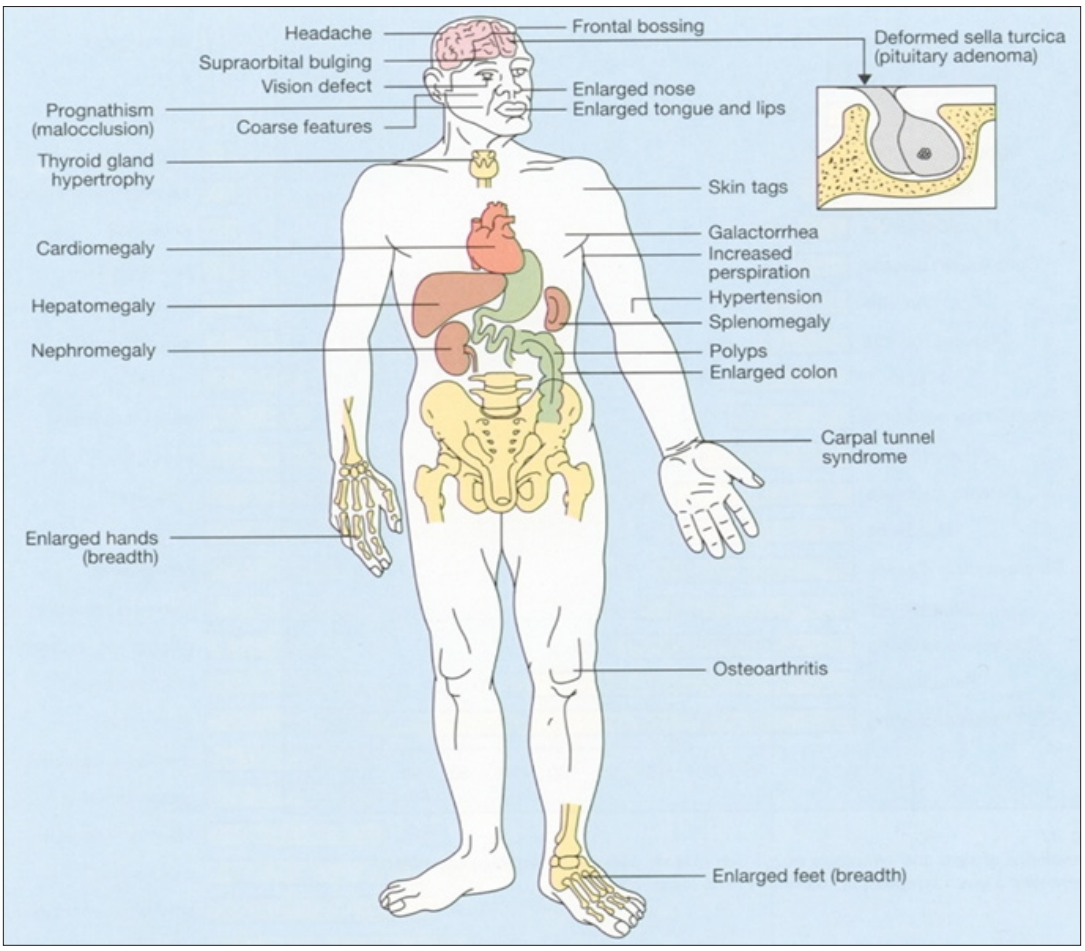


Pathogenesis of Acromegaly



Clinical Features of Growth Hormone Excess

- Acral enlargement and/or coarse features
- Sweating
- Menstrual disorder
- Headaches
- Arthritis/carpal tunnel syndrome
- Diabetes or pre-diabetes
- Soft tissue hypertrophy
- Impotence of decreased libido
- Hypertension
- Visual field defects
- Obstructive sleep apnea
- Galactorrhea
- Coronary artery disease



Acromegaly: Signs and Symptoms

Most common clinical features are[1]:

1. acral enlargement = 86%
2. maxillofacial changes = 74%
3. excessive sweating = 48%
4. arthralgias = 46%
5. headache = 40%
6. visual deficits = 26%
7. fatigue = 26%
8. Weight gain 18%.

Less often and overlooked presentation[1]

1. Hirsutism
2. Oligo-amenorrhea
3. Carpal-tunnel syndrome
4. OSA
5. Secondary PCOS- in up to 50% of patients

Mechanism of HIRSUTISM IN ACROMEGALY[1]

1. Decreased SHBG by excess GH and increased Free Testosterone
2. Insulin resistance caused by excess GH leads to increased insulin which stimulates ovarian theca cells to synthesize more androgens as well as decreases SHBG and increases Free Testosterone

Acromegaly - Diagnosis

IGF-1

- Simple screening test
- Reference range: Matched by age / gender

Growth hormone suppression test

Confirmatory test

- OGTT with GH levels - should suppress <1 µg/L
- 75g of glucose
- GH + glucose levels every 30 minutes x 2 hours

MRI

- If negative: Send GHRH level

Acromegaly incidence is 0.2-1.1 cases /100,000 people[2,3]. It is diagnosed clinically and biochemically[4,5,6]. Because GH is pulsatile throughout the day, it is not useful for diagnosis, so measurement of serum IGF-1 is used instead for screening for Acromegaly. Has longer half-life. For Age/sex-matched value needs to be adjusted.

If IGF-1 is above normal for the age and gender the excess GH is confirmed with an oral glucose tolerance test because glucose normally suppresses GH levels to less than 1 ng/mL (1 µg/L) or bellow 0.3 ng/ml on ultrasensitive assay. GH levels equal or greater than 1 ng/mL (1 µg/L) or equal to or greater than 0.3 ng/ml on ultrasensitive assay are diagnostic of GH excess.

A pituitary MRI should be obtained once GH excess is confirmed biochemically. If MRI negative for adenoma HP area check GHRH-causes acromegaly in 5% of the cases with acromegaly due to GHRH tumors or neuroendocrine tumors secreting GHRH. Usually, acromegaly is caused by macroadenomas! The diagnosis is done usually late

Consultation with an endocrinologist is recommended if IGF-1 is elevated. Also ruling hypopituitarism should be done when adenoma is confirmed! Usually, Dynamic contrast-enhanced MRI has the highest yield for finding small HP adenomas-microadenomas. A 5-year delay in DX of Acromegaly is usually the rule!

When the DX of Acromegaly is confirmed[7]

1. As soon as possible perform a colonoscopy. Increased incidence of colonic polyps. Increased incidence of colonic CA. After removal of polyps if IGF-1 is normal the colonoscopy can be repeated in 10- years. If IGF-1 is increased we need to discuss with the GI specialist when to repeat colonoscopy.
2. Also, increased incidence of thyroid nodules and thyromegaly- USG thyroid needs to be done.
3. ECHO- if heart complaints or risk factors- HTN etc.

Further Assessment

Acromegaly

- Visual fields - if abuts optic chiasm
- Other pituitary hormones
  - 50% co-secretes prolactin
  - Frequent hypogonadism, other hormone deficiency
- Blood pressure, glucose / lipid measurements
- Clinical evaluation for cardiac disease, OSA, thyroid nodule / enlargement

A 25-year-old lady came to our office with complaints of secondary amenorrhea that started 6- months ago and hirsutism. She was treated by her OBGYN physician for PCOS with OCPs and cosmetic measures for her hirsutism. Her Ferriman-Gallwey score was 12(6-8 and above suggests hirsutism). Because of a lack of improvement, she came to see an endocrinologist. On further questioning, she admitted headache, increased sweating, and numbness of the fingers usually after sleep. She noticed increased puffiness of her face and fingers. Also had an enlarged thyroid gland and the ultrasound showed multinodular goiter. From laboratory studies, we have found that she had pre-DM type 2 and increased phosphate level, nl TSH, with mildly decreased FT4, normal total testosterone, mildly increased Free testosterone, low normal LH/FSH, and low estradiol.

What is your next step in investigating this patient?

A. Check IGF1 and ProlactinB. Obtain an ultrasound of her ovaries to r/o testosterone-secreting tumorC. Obtain CT adrenals and check DHEAS to r/o androgen-secreting tumorD. Obtain an MRI of her hypophyseal area.

What is your next step in investigating this patient?

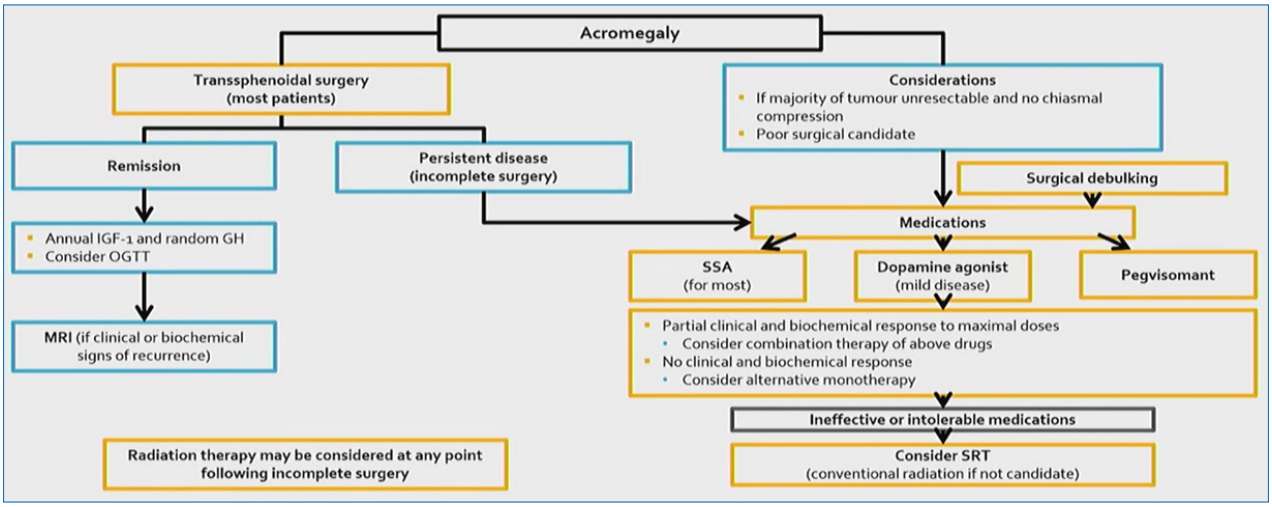
- Check IGF1 and Prolactin
- Obtain an ultrasound of her ovaries to r/o testosterone-secreting tumor
- Obtain CT adrenals and check DHEAS to r/o androgen-secreting tumor
- Obtain an MRI of her hypophyseal area

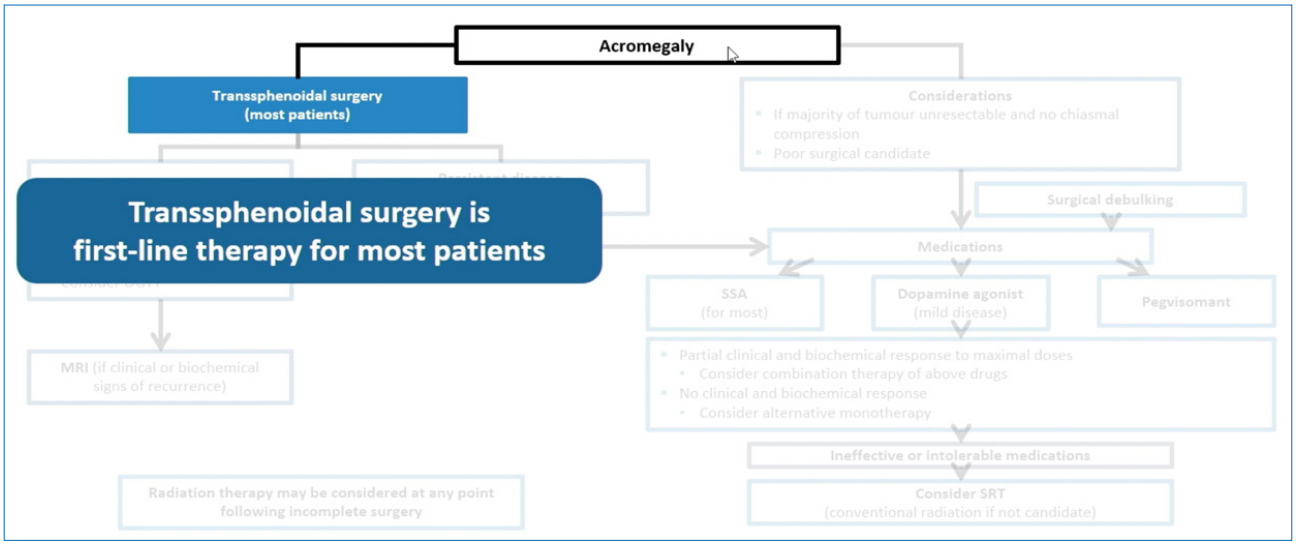
The IGF–1 level was increased twice the upper limits of normal for her age and sex on 2- occasions. Serum Prolactin was normal.

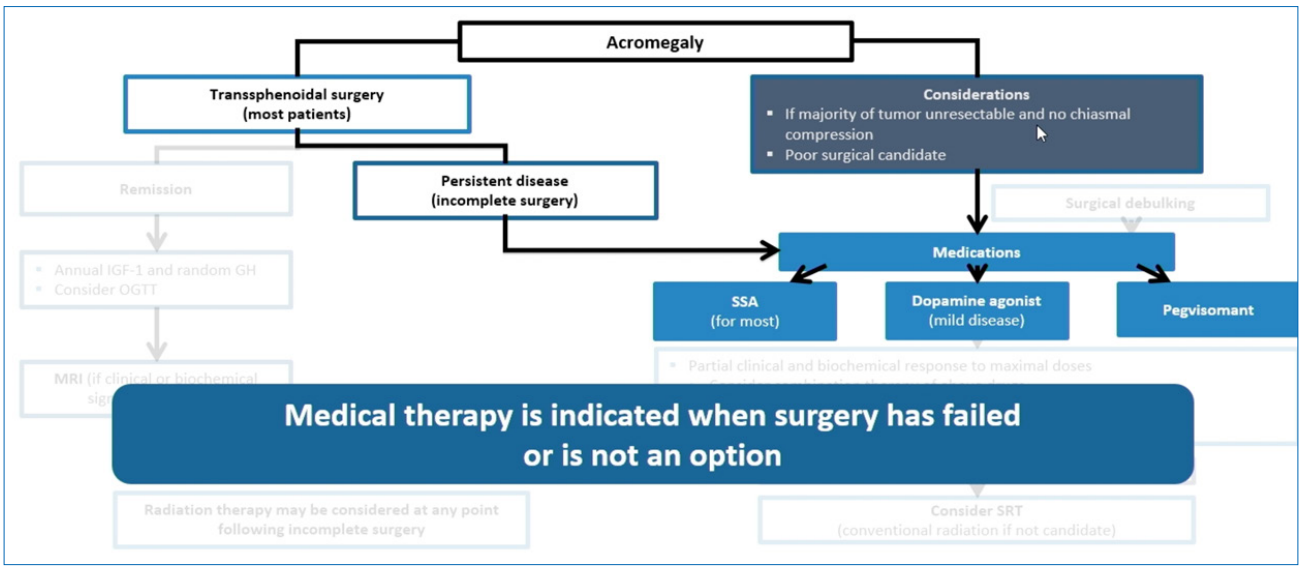
What is your next step?

- Obtain pituitary MRI
- Obtain ultrasound of the ovaries to r/o PCOS or ovarian tumor
- Obtain 2-hour OGTT and GH levels
- Check 17-OH progesterone to r/o CAH as a cause of her hirsutism and amenorrhea

Management of Acromegaly







Treatment of Acromegaly - Surgery

Transsphenoidal surgery

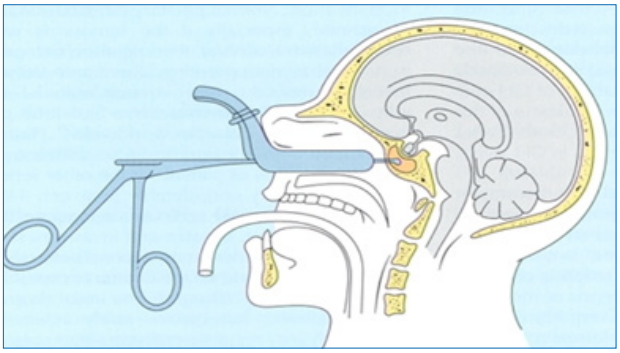
Pre-treatment with medications not usually indicated unless severe pharyngeal thickness or high-output heart failure

12 weeks later

- Cure - IGF-1 WNL and random GH <1 µg/L
- Monitor annually

Surgical cure

- 85% micro
- 40 - 50% macro (75% of the cases are macro)

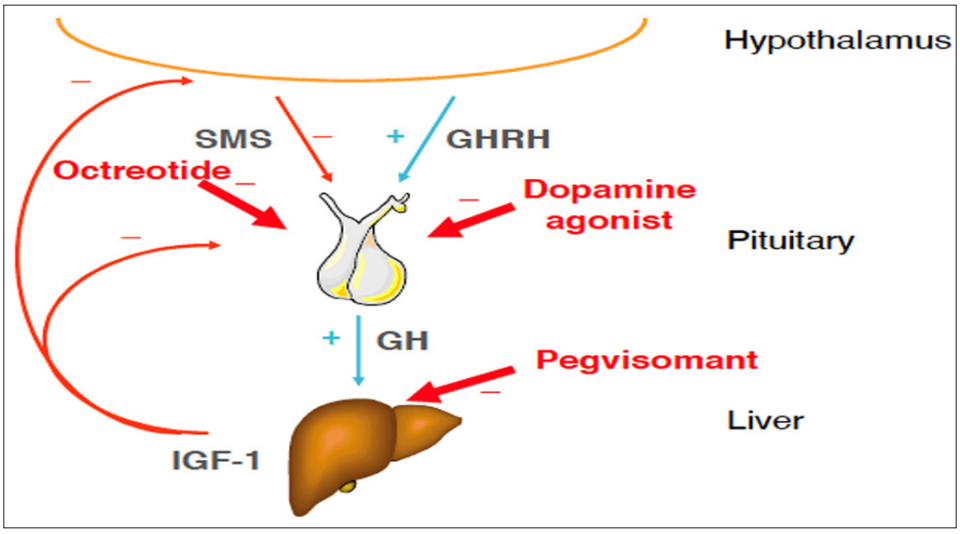


Management of Acromegaly

- Visual fields - if abuts optic chiasm
- Other pituitary hormones
- 50% co-secretes prolactin
- Frequent hypogonadism, other hormone deficiency
- Blood pressure, glucose / lipid measurements
- Clinical evaluation for cardiac disease, OSA
- Echocardiogram
- Colonoscopy - increased risk of polyps and colorectal cancer
- Cardiac disease

Pretreatment with SRLs is done if pharyngeal hyperplasia, high cardiac output CHF, uncontrolled HTN, and or DM.

In tumors if first surgery(debulking) followed by medical treatment improves response to SRLs- up to 70% control of Acromegaly.



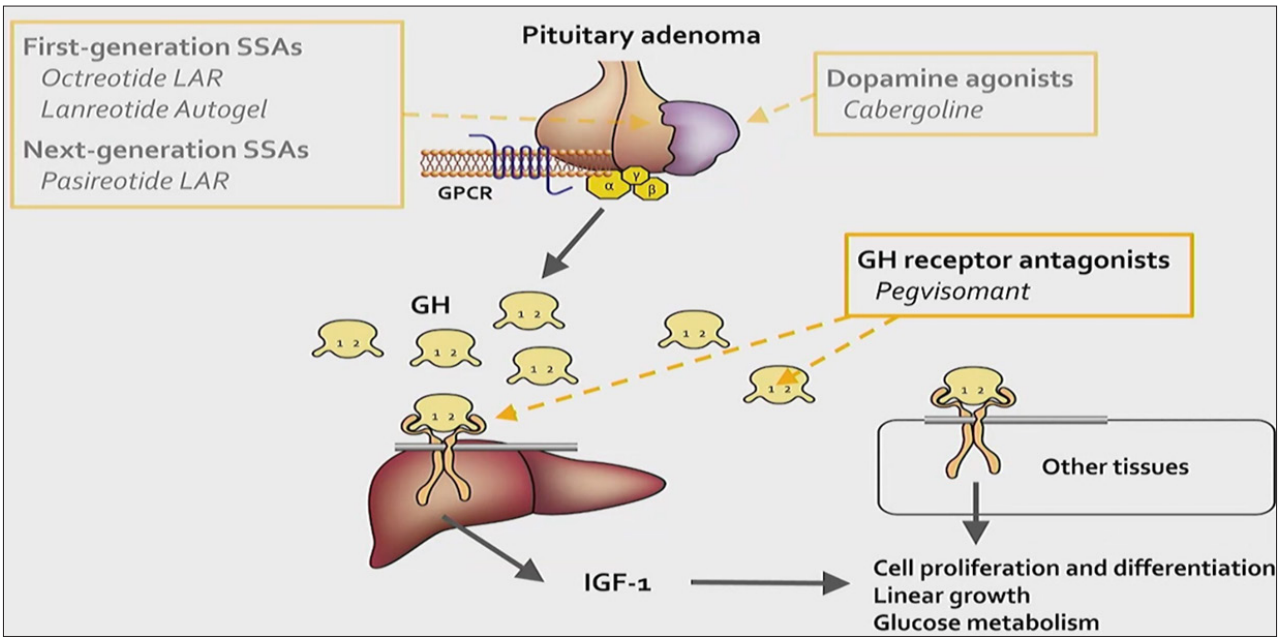
Treatment of Acromegaly - Medical

- Medical therapy if persistent disease or poor surgical candidate/majority of tumor unresectable
- Elevated IGF-1 or random / OGTT-suppressed GH > 1 µg/L
- Surgical debulking increases efficacy of medical therapy
- Consider stereotactic radiotherapy (or conventional radiotherapy) if residual tumor mass after surgery and medical therapy not successful

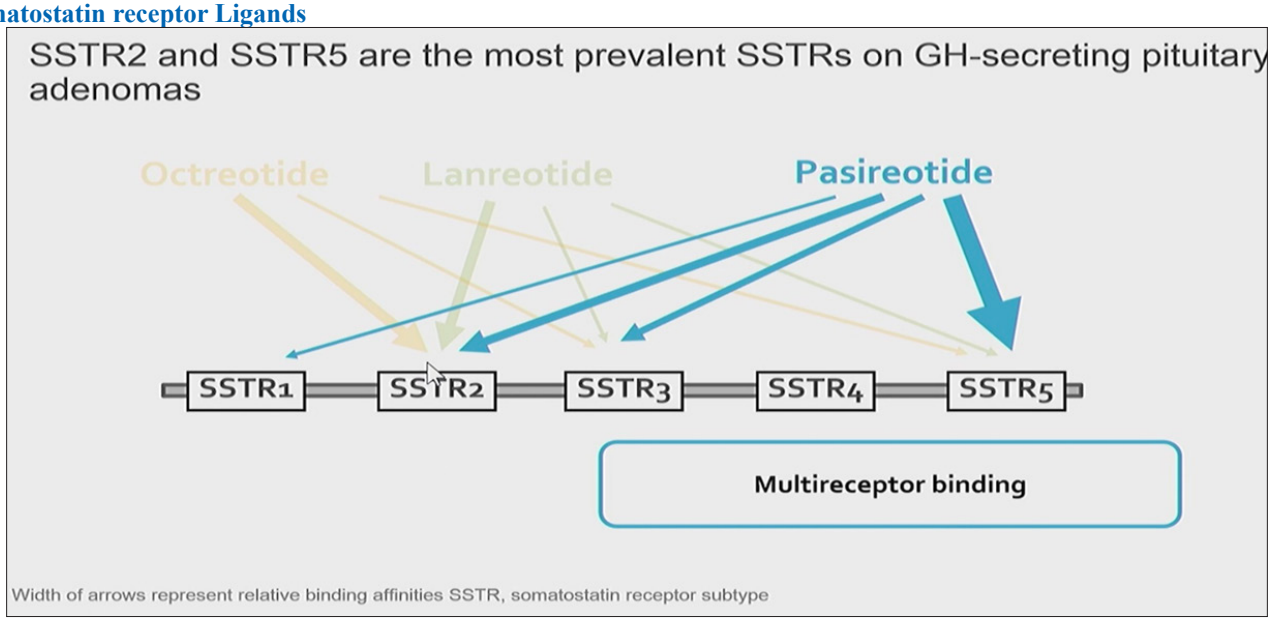
Medical management of persistent disease

- First-generation somatostatin receptor ligands (SRLs)
  - Octreotide LAR 10-40 mg monthly
  - Lanreotide depot 60-120 mg monthly-q2months
- Pasireotide LAR 40-60 mg monthly
  - Side effects: GI - cramps, flatulence, diarrhea, gall stones / gall bladder sludge. Hyperglycemia
- Cabergoline - DA
  - Mild disease (IGF1 <2.5 ULN)
  - Effective with elevated or normal prolactin
- Pegvisomant 10 - 30 mg daily
  - pre-existing clinically relevant impaired glucose metabolism

Medical Therpay of Acromegaly



Somatostatin receptor Ligands



Granulation pattern of the GH secreting Adenomas and its effect on clinical presentation and treatment

1. Densely granulated GH-secreting tumors occur usually after the age of 50, grow slowly, have lower intensity on T2 MRI images, contain more SSTR2 expression and respond well to First generation SRLs-Octreotide- LAR and Lanreotide Auto gel as well to oral Octreotide. If those tumors lack SSTR5 they do not respond to Second generation SRL- Pasireotide LAR but to the first generation SRLs and oral octreotide.
2. Sparsely Granulated GH secreting tumors occur usually before the age of 50, are more aggressive, have higher cavernous and sinus invasion rates, are larger at DX, have higher mitotic index, have higher intensity on T2 MRI images, have lower expression of SSTR2 and higher of SSTR5, they have poor response to first generation SRLs and respond primarily to Pasireotide LAR which affects to greatest extend the SSTR5. In younger than 30 years patients with FH of the disease look for genetic cause- germline mutation- AIP. Those tumors have higher recurrence rates based on some studies.

Summary Of The Treatment Options For Acromegaly[6,8]

1. First line- Transsphenoidal surgery of the GH-secreting Adenoma or transcranial resection if the tumor is big. Usually macro adenoma. If residual tumor – reoperation if possible! This is valid if accessible for surgery tumors. If not accessible- in sphenoidal sinus majority of the tumor- medical therapy is the first choice. Consider medical therapy before surgery if significant pharyngeal thickening or high cardiac output CHF. In microadenoma surgery is effective 79-91% of cases, but in macro-50-60%.
2. Second line if 1 can not control the disease- Somatostatin analogs- Octreotide LAR, lanreotide Autogel, Pasireotide. Side effects- GI with abdominal pain, diarrhea, increased BS- decreases the secretion of Insulin, especially with Pasireotide-57% glycemic abnormalities and Gall bladder stones. Effective in 40-60% of cases depending on the study in normalization of IGF-1 and GH <2.5, but if first surgical debulking -70%. The response depends on the size of the GH-producing adenoma of the HP and the granulation pattern. If no or poor response to Octreotide LAR or Lanreotide Autogel switch to Pasireotide.
3. Dopamine agonist- Cabergoline leads to a response of around 34% in patients with mild disease –IGF1 less than 2.5 NL.

Treatment options for acromegaly c/o:

4. Pegvisomant- GH receptor blocker. Monitor for growth t the GH-secreting adenoma. This usually happens in 3-5% of the cases. Controls IGF1 in 90% of the cases. A side effect is LFT elevation-monitor monthly. Elevation above 3 times nl in 1.2%
5. If some response to maximum dose monotherapy try combined therapy- SRLs and Pegvisomant normalize IGF1- 95%- weekly PegvisomantV s.c. 60-150mg and daily /weekly dose SRLs.
6. If no effect in monotherapy with one drug try monotherapy with another drug. Remember that morbidity and mortality are associated with the level of IGF1 after treatment – needs to be nl for the age and gender and GH needs to be less than 1 ng/ml baseline or after OGTT- Oral Glucose tolerance test.
7. Stereotactic radiosurgery- in difficult to treat disease. Up to 50% of another hormonal deficiency in 10-15 years. Starts working in 2-3 years. Might cause intrasellar malignancies rarely.

Indications for Radiotherapy in Acromegaly

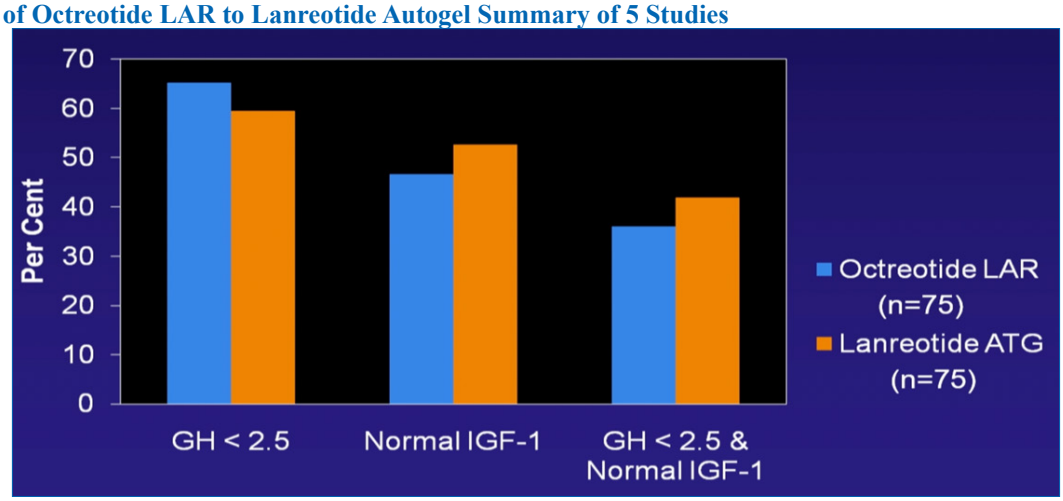
- Persistent, symptomatic excess hormone secretion despite surgery and/or medical therapy
- Often used in conjunction with
- medical therapy
- Primary therapy when surgery contraindicated
- Currently, focused, stereotactic radiotherapy preferred

Stereotactic Radiotherapy for Acromegaly

Meta-Analysis of 1533 patients treated in various series

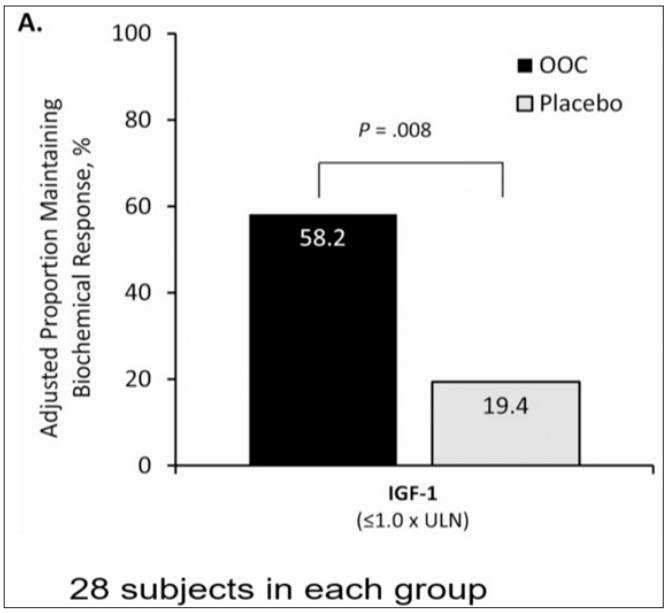
	Endocrine Remission	Endocrine Control	Local Control	Hypopituitarism
5 years	43.2%	55.0%		
10 years	56.9%	69.7%	92.8%	26.8%

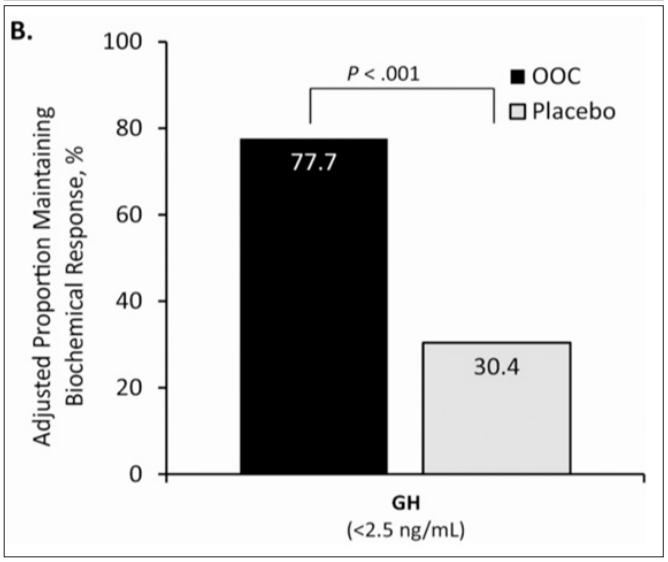
Comparison of Octreotide LAR to Lanreotide Autogel Summary of 5 Studies



OPTIMAL STUDY - Oral Octreotide

Proportion of patients who had biochemical response at the end of double-blind placebo-controlled portion of study.





Oral Octreotide (Mycapssa)

INDICATIONS AND USAGE

MYCAPSSA...is indicated for long-term maintenance treatment in acromegaly patients who have responded to and tolerated treatment with octreotide or lanreotide

FDA approval June 26, 2020

Improvement with the treatment of acromegaly

1. OSA, snoring, the large tongue
2. HTN improves. GH activates RAAS and increases sodium and water retention in the kidneys. After treatment increased diuresis
3. Improved BMD- Check DEXA in 18 months and decreased FX risk
4. Improves DM
5. Improves early arthritis, but not the advanced one
6. Decreases sweating

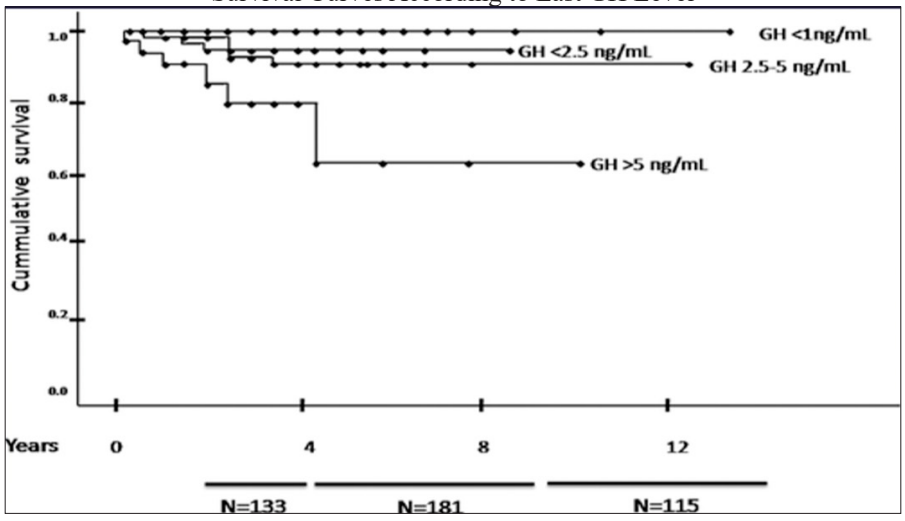
Acromegaly: Prognosis

Prognosis[5]:

- The vast majority of acromegalic patients have very good control of GH/IGF-I secretion and no problems relating to tumor growth
- If left untreated = die about 10 years earlier than healthy subjects
- Standardized mortality rate (the ratio of observed mortality in the
- 60% of death due to CV disease
- 25% = respiratory
- 15% cancer
- acromegalic population to expected mortality in the general population) ranges from 1.2 to 3.3.
- Life expectancy outcomes can be stratified according to the post-treatment GH concentration: if GH secretion is controlled, life expectancy merges with that of the matched general population
- High GH and IGF-I concentrations, arterial hypertension, and cardiomyopathy are factors in a poor prognosis
- While the duration of symptoms and other factors(diabetes, lipid disorders and cancer) are less important

Acromegaly (n=442)

Survival Curves According to Last GH Level



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