HORMONAL WOES - FINDING THE RIGHT BALANCE
2023 PATIENT FAMILY GATHERING

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BIOMED VALLEY™ DISCOVERIES

MAYO CLINIC LABORATORIES

ERDHEIM-CHESTER DISEASE GLOBAL ALLIANCE

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Hormonal Woes- Finding the Right Balance

Endocrine Disorders in Erdheim-Chester Disease

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NIH Intramural Research Program
Our Research Changes Lives

Q1 How many of you

1. Know about endocrine disorders?

2. Know someone with an endocrine disorder?

Q2 What percentage of ECD patients have an endocrine disorder?

A. 30%
B. 50%
C. 80%
D. >90%

Q2 What percentage of ECD patients have an endocrine disorder?

A. 30%
B. 50%
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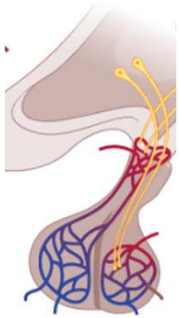
Endocrine System

- **Hormones**: Chemical messengers that control multiple functions of the body, such as energy, metabolism, sleep, diet, reproduction and bone health. E.g.: Insulin, thyroid, testosterone, cortisol

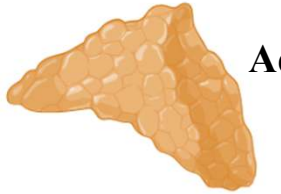
- **Endocrine Glands**: Organs that secrete hormones into the bloodstream.



Hypothalamus

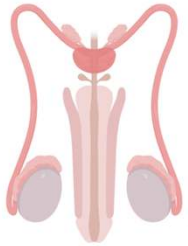
Pituitary Gland

Thyroid Gland



Adrenal Gland

Ovaries

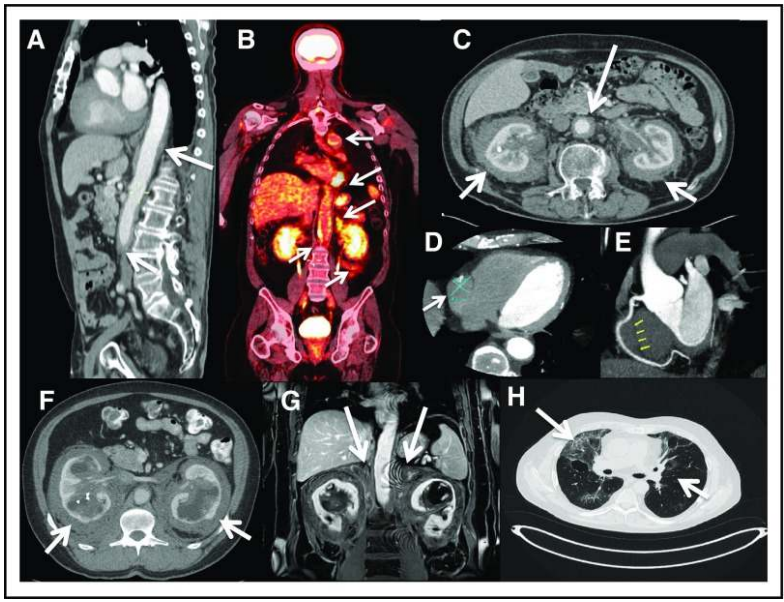


Testes

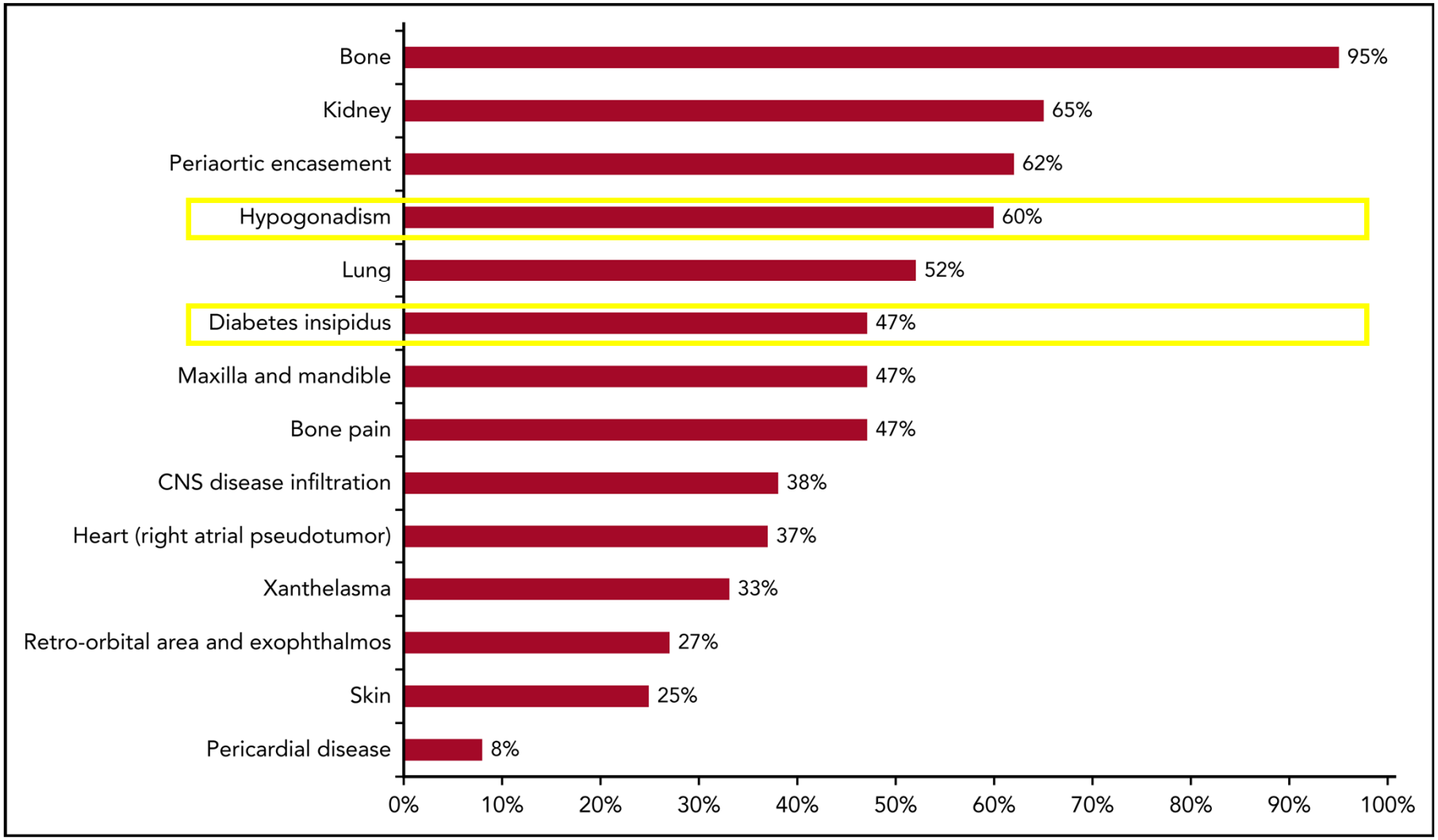
Erdheim Chester Disease

- First described by Erdheim and Chester in 1930
- A rare form of non-Langerhans cell histiocytosis
- Affects- brain, bone, blood vessels, heart, skin etc

- **Hormone dysfunction** has been reported in **>90%** of those with a comprehensive evaluation. (*Courtillot* et al. 2016)



Estrada-Veras et al. Blood 2017

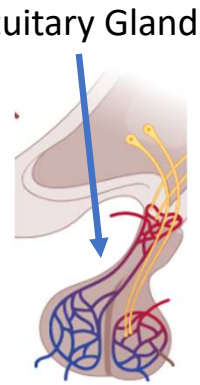


Data from Estrada-Veras et al. 2017 Published: Goyal et al. 2020

General Principles of Managing Endocrine Disorders in Erdheim-Chester Disease

1. Endocrine disorders are among the commonest and earliest manifestations of ECD
2. All patients with ECD should undergo annual hormone testing
3. ECD consensus committee recommends MRI pituitary in all ECD patients
4. Most hormone disorders persistent despite molecular treatment of ECD and may require lifelong treatment
5. Early referral to appropriate specialists such as endocrinologists can significantly alleviate morbidity and improve quality of life
6. Patient education, counselling and partnership are key

Central Diabetes Insipidus (DI) (Arginine Vasopressin Deficiency)



- Different from Diabetes Mellitus (elevated blood glucose)!!
- A deficiency of the hormone arginine vasopressin secreted by the pituitary gland
  - Vasopressin maintains water balance
- DI occurs in > one-third of patients with ECD* and may be the only feature preceding other ECD symptoms by years
- Associated with abnormal findings on pituitary imaging*
- DI persists even after successful treatment of ECD and may require lifelong therapy

*Shekhar et al. 2021, Courtillot et al. 2016

Central DI(AVP Deficiency) Management

Diagnostics

Symptoms and Signs

Increased thirst, and excessive urination (>3L/day) Waking up at night to pass urine Dehydration and electrolyte imbalances.

Laboratory

Increased blood sodium and osmolarity, diluted urine (low osmolarity), low blood copeptin

Brain Scan (MRI)

Abnormal Pituitary MRI
Absent Pituitary Bright Spot

Treatment-Desmopressin

Patient education, one a week drug holiday

100mcg-200mcg tablets (start with 50mcg) OR 60-120mcg liquid, 1-2 times a day

5-10mcg nasal spray 1-2 times a day

1-2mcg subcutaneously or intravenously

Adrenal Insufficiency (AI)

Adrenal Gland

- A deficiency of the stress hormone: Cortisol ± Aldosterone
- Both are secreted by the adrenal gland
- Cortisol: maintains stress response, blood pressure other vital functions
- Aldosterone: maintains blood pressure and sodium levels
- Adrenal Gland involvement: 31.6%; 6% have adrenal insufficiency
- Six times higher odds of adrenal involvement in *BRAF* V600E pathogenic variants
- Use of exogenous glucocorticoids (steroids) also leads to suppression of cortisol (secondary AI)

*Hannah-Shmouni et al. 2020, Goyal et al. 2020

Adrenal Insufficiency Management

Diagnostics

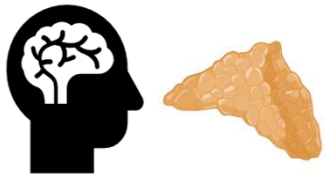
Symptoms and Signs

Non steroid users: Fatigue, weight loss abdominal pain, nausea, leg cramps, low blood pressure, crises, skin pigment changes

Steroid users: diabetes, weight gain, facial rounding, fat pad on the neck, stretch marks, high BP

Laboratory

Low 8 am blood cortisol, high or low ACTH values (cause dependent), abnormal response to ACTH stimulation test



Imaging

Abnormal Adrenal CT scan
Abnormal Pituitary MRI

Treatment and Counseling

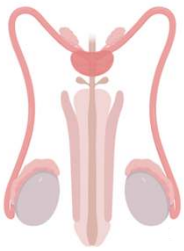
Patient education about the disease, sick day rules and medical alert bracelet/card

Oral Hydrocortisone- dose depends on body weight and height, disease severity
Fludrocortisone: if primary AI

100 mcg subcutaneously
In case of emergency/illness

Hypogonadism

Ovary



Testes

- A deficiency of sex hormones with/without infertility
- **Men:** low testosterone (T) levels due to testicular effects
- **Women:** abnormal estrogen levels due to ovarian effects

- Hypogonadism present in 20-60% of patients with ECD
- Could be related to
  - Testicular or ovarian infiltration: primary hypogonadism
  - Pituitary gland dysfunction: central hypogonadism
- Elevations of prolactin can precipitate or worsen hypogonadism
- Use of exogenous glucocorticoids (steroids) and chronic illness can suppress T

Estrada-Veras et al. 2017, Courtillot et al. 2016

Hypogonadism Management

Diagnostics

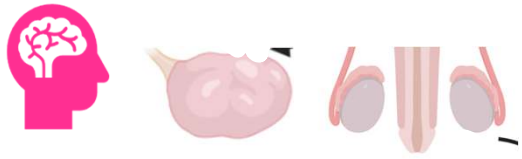
Symptoms and Signs

Men: Fatigue, low libido, loss of muscle mass, depression, weight gain, sexual dysfunction, infertility

Women: irregular/absent periods, menopause, bone fragility, infertility

Laboratory

Low 8 am blood T x 2, low blood estradiol, high or low LH/FSH (cause dependent) .



Imaging

Abnormal testicular or ovarian ultrasound
Abnormal Pituitary MRI

Treatment and Counseling

Patient education and discussion of risks and benefits of treatment

Men: Injectable or oral testosterone (or patches/gels) with dose titration to restore T
Women: hormone replacement (or oral contraceptives). Fertility management.

Regular monitoring: hemoglobin, prostate and bone health and clotting risks

Hypothyroidism

Thyroid Gland

- A deficiency of thyroid hormones: T3 and T4
- Symptoms are non-specific and overlap with those of other diseases
- Almost one third (28%) ECD patients have hypothyroidism
- Could be related to
  - Thyroid gland infiltration: primary hypothyroidism
  - Pituitary gland dysfunction: central (secondary) hypothyroidism
- Some treatments may contribute to thyroid dysfunction:
  - steroids and interferon therapy

*Shekhar et al. 2020, Courtillot et al. 2016

Hypothyroidism Management

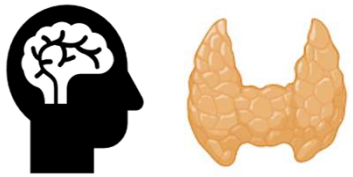
Diagnostics

Symptoms and Signs

Non steroid users: Fatigue, weight gain, mental fogginess, hypercholesterolemia, dry skin, hair loss, hypertension, can worsen quality of life

Laboratory

Blood levels of TSH, free T4 and total T3



Imaging

May reveal pituitary destruction or thyroid gland infiltration

Treatment and Counseling

Oral levothyroxine- dose depends on body weight; to be taken empty stomach

Dose to be adjusted to attain normal

- TSH (primary hypothyroidism)
- Or free T4 (central hypothyroidism)

Other Endocrine Disorders

Metabolic Syndrome and Diabetes Mellitus

- Frequency unknown but may contribute to the burden of disease in ECD
- Can be worsened due to the disease or its treatment
- Needs to be screened for in all patients

Growth Hormone Deficiency

- Likely to be very common in ECD and may contribute to some symptoms
- Unfortunately, GH therapy cannot be administered in active neoplasms

Osteoporosis

- Bone involvement is common, but osteoporosis burden is unknown
- Should be screened for in an age and sex-appropriate fashion
- Especially those receiving treatments that impact bone (steroids and chemotherapy)

ECD Consensus recommendations (2020)	Category of consensus*
Diagnosis	
ECD without any bone lesions can occur (<10%) but should only be considered in the context of suggestive histopathology or highly characteristic nonosseous lesions (ie, perinephric stranding, periaortic infiltrates, right atrial pseudotumor, **or a combination of these with or without central diabetes insipidus**) and ideally with supportive mutational data (BRAF or MAPK-ERK pathway mutations)	A
MRI of the brain with gadolinium is recommended in all patients at diagnosis	A
Laboratory studies are performed to assess for renal insufficiency, cytopenias, markers of inflammation (C-reactive protein), and **evidence of endocrinopathy and anterior pituitary function**	A
Treatment	
Systemic corticosteroids, surgery, and radiation therapy may be used to relieve edema or acute symptoms, but are **not recommended** as monotherapies for ECD	A
Response assessment and monitoring	
Organ-specific imaging of involved disease sites (CT or MRI) should be performed every 2-6 mo initially after beginning treatment of response assessment; once best response is established on 2 scans and disease is stabilized with steady dose of drug, the frequency of imaging can be individualized, ranging from every 6 mo to longer intervals; a separate CT may not be necessary if performed in conjunction with FDG-PET	B
Endocrinopathies persist or can develop despite treatment of ECD; therefore, annual endocrine evaluation is recommended	A

Resources

- American Association of Clinical Endocrinologists

https://pro.aace.com/resources?keys=&field_disease_state_content_t_value%5BGuidelines%5D=Guidelines

- Endocrine Society Guidelines

https://www.endocrine.org/clinical-practice-guidelines

- Erdheim Chester Disease Guidelines

https://ashpublications.org/blood/article/135/22/1929/452713/Erdheim-Chester-disease-consensus-recommendations

QUESTIONS?