Abnormalities of Pituitary Imaging and Associated Endocrine Disorders in Erdheim-Chester Disease

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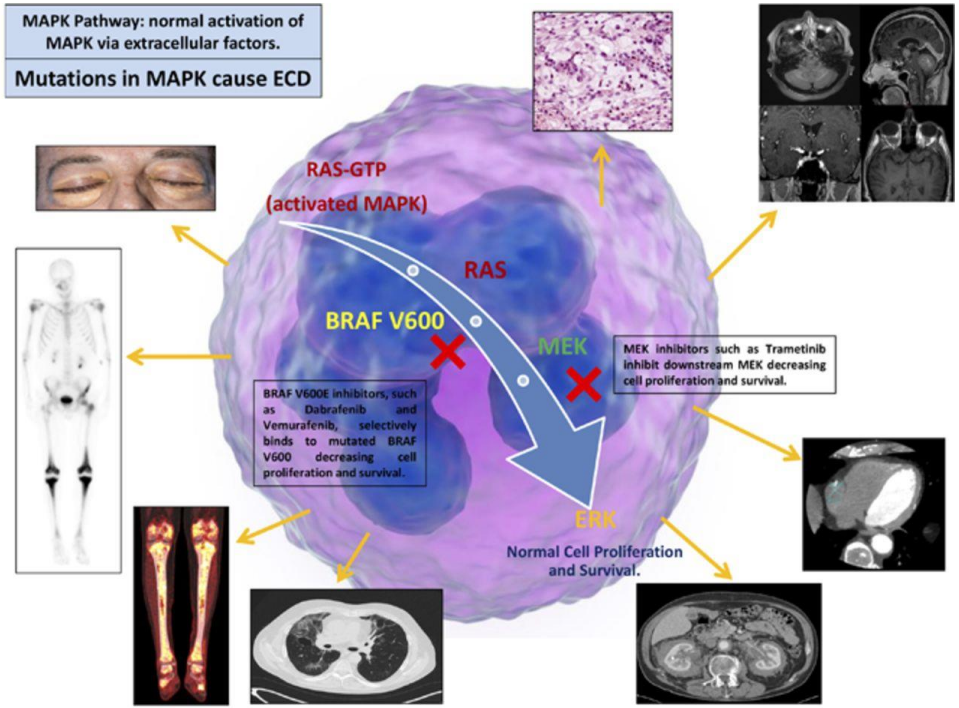
No Conflict of Interest. **Co-senior authors*

Erdheim Chester Disease

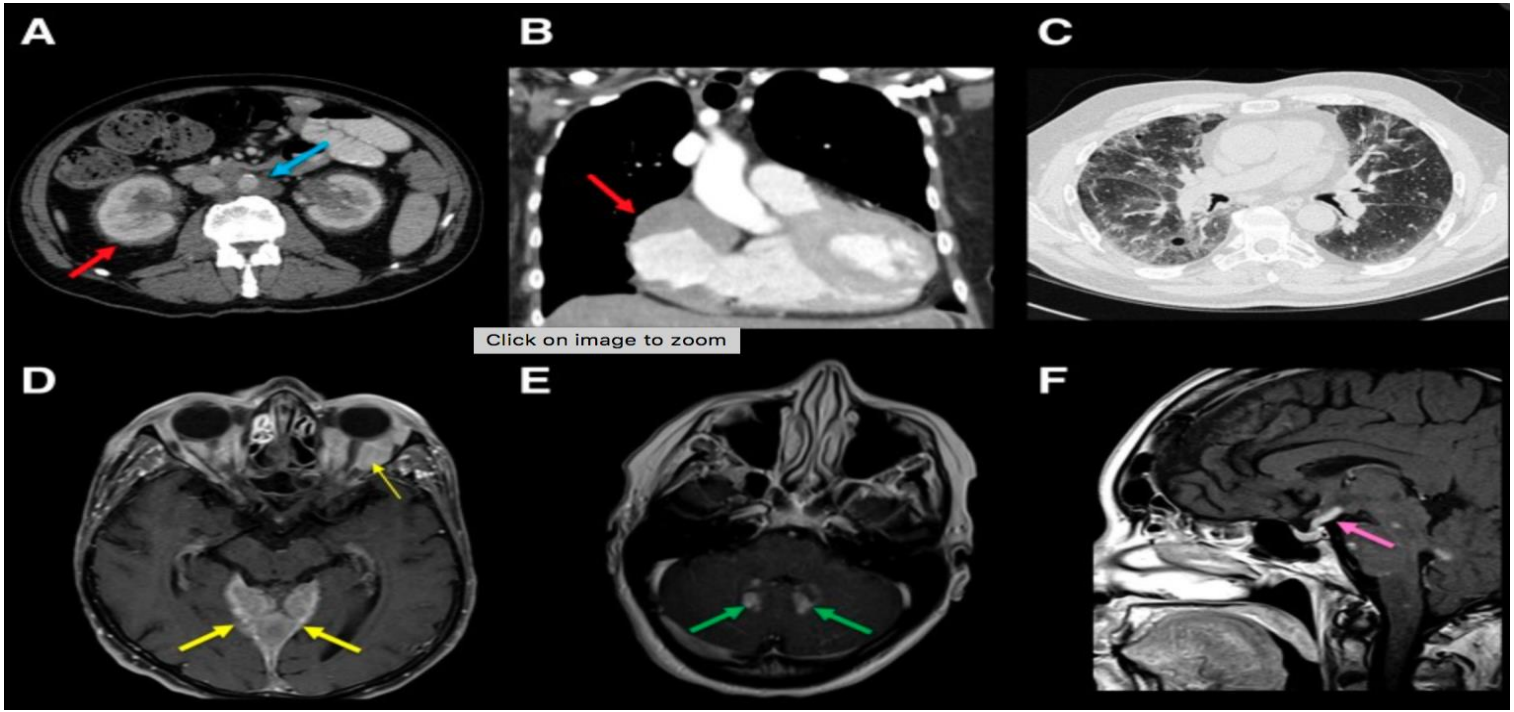
- A non-Langerhans histiocytosis <1000 cases worldwide
- Initially described by Erdheim and Chester as lipoid granulomatosis in 1930
- Disruptions in molecular genetic pathways such as *BRAF* V600E and *MAP kinase* in a group of hematopoietic cells lead to their
  - increased production
  - prolonged survival
- ECD leads to a wide variety of endocrinopathies
  - Hypothyroidism, Diabetes Insipidus, Adrenal Insufficiency, Hypogonadism etc.

Pathogenesis



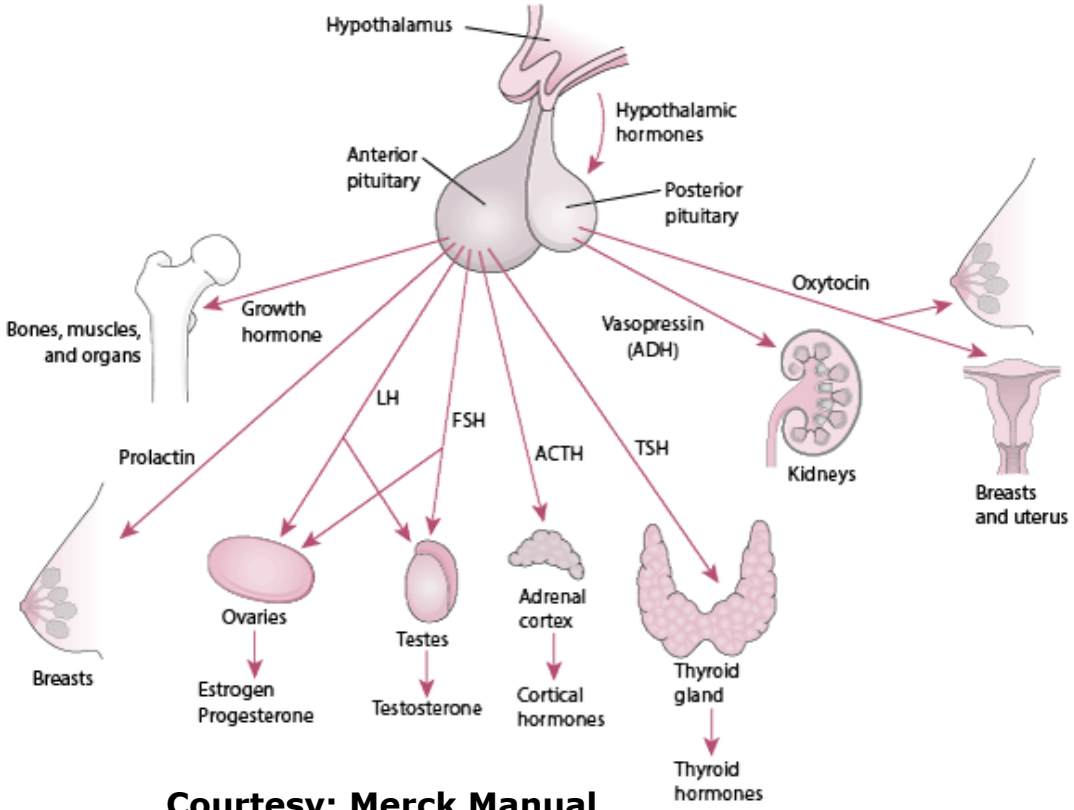
Juvianee I. Estrada-Veras et al. *Blood advances* 2017.

Commonly affected organ systems



Diamond EL. *Blood* 2014.

Hypothalamus, Pituitary Gland and Endocrine Axes



Courtesy: Merck Manual

Hypothalamic-Pituitary Endocrine Axes in ECD

- The pituitary gland is the master endocrine organ responsible for the maintenance of a host of endocrine functions
  - Deficiency of Vasopressin: Central Diabetes Insipidus (Arginine Vasopressin Deficiency)
  - Deficiency of Thyroid, Sex Hormones and Adrenal Hormones: Hypothyroidism, Hypogonadism and Adrenal Insufficiency

- In ECD, a high burden of histiocytic infiltration in the CNS→ pituitary destruction

- These may manifest as **abnormal pituitary imaging (API)**, with or without biochemical abnormalities, but their frequency and characteristics have not been extensively studied

- Unknown: Association of API with sex, age, BMI, hypothalamic–pituitary hormone dysfunction, BRAF V600E status, and inflammation (hs-CRP levels)

Hypothesis

There is a high prevalence of abnormal pituitary imaging in ECD that is associated with a higher burden of pituitary endocrine disorders

Study Aims

1. To determine the frequency of pituitary imaging abnormalities in patients with biochemically confirmed Erdheim-Chester disease

2. To assess the correlation between abnormal pituitary imaging with subject demographics, genetics and endocrine disorders

Methods: Overview

- Study Design: A cross-sectional analysis of a larger National Institutes of Health natural history study
- Site: National Institutes of Health Clinical Center, Bethesda, Maryland USA
- Time Period: 2011-2018
- Subjects: Biopsy-proven ECD subjects

Methods: Procedures

❖ Diagnosis of ECD

- Biopsy specimens for all enrolled subjects were reviewed by a pathologist who confirmed the diagnosis

❖ Genetics

- All subjects underwent screening for *BRAF* V600E variants. Those without *BRAF* V600E pathogenic variants were tested for *KRAS, NRAS, MAP2K1, PIK3CA,* and *ARAF* (MAP Kinase) gene variants

❖ Imaging

- MRI of the pituitary (±contrast) in 56 subjects and the remaining 5 had CT scans of the sella.
- The scans were reviewed and reported by a certified NIH neuroradiologist and confirmed by neuroendocrinologists (FHS, SS) with expertise in pituitary disorders.

Methods: Procedures

❖ **Endocrine Tests/Diagnosis**

- Hypothyroidism: low free and total T4, TSH
- Diabetes Insipidus: Based on clinical presentation/biochemical features (Serum Na, osmolarity)
- Hypogonadism: Low testosterone (8 am) or estradiol (with abnormal gonadotropins)
- Others: Adrenal insufficiency, growth hormone testing.

❖ **Number of endocrine deficits**

- the sum of all pituitary-related endocrine deficits

Study Population (n=61)

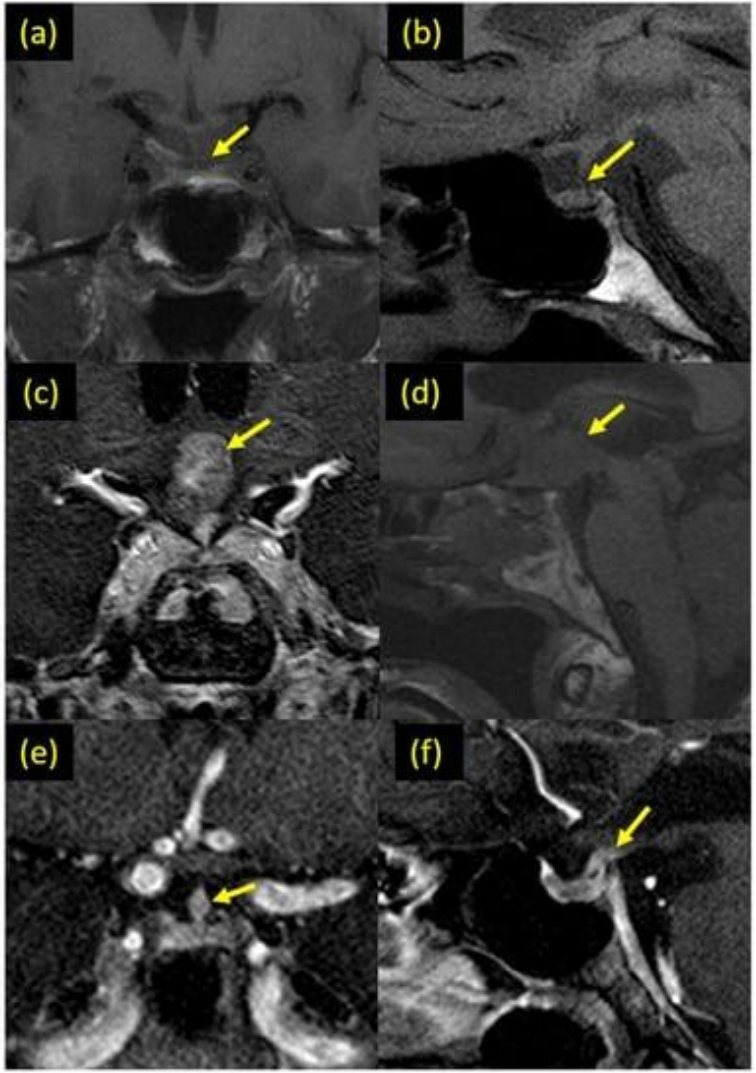
	Study Cohort (ECD) (n=61)
Age, mean (SD), years	54.3 (10.9)
Sex, Female No. (%)	15 (24.6)
BMI, median (IQR)	27.8 (24.8-32.9)
BRAF pathogenic variant, positive No. (%)/n	31 (54.4)/57
Panhypopituitarism No. (%)	9 (14.8%)
Diabetes insipidus No. (%)	22 (36.1%)
hsCRP, median (IQR)/n, mg/L	12.2 (3.1-45.4)
ESR, median (IQR)/n, mm/h	23 (11.0-38.0)
Number of deficits, median (IQR)	1.0 (0-2.0)

Higher Endocrine Dysfunction in Abnormal Pituitary Imaging

	Abnormal Pituitary Imaging (n=29)	Normal Pituitary Imaging (n=32)	P Value
Age, mean (SD), years	**50.6 (11.7)**	**57.7 (9.0)**	0.010
Sex, Female No. (%)	7 (46.7%)	8 (53.3%)	1.0
BMI, median (IQR)	27.8 (24.7-33.3)	28.4 (25.3-32.7)	0.69
BRAF pathogenic variant, positive No. (%)/n	16 (51.6%)	15 (48.4%)	0.60
Panhypopituitarism No. (%)	**9 (100.0%)**	**0**	<0.001
Diabetes insipidus No. (%)	**18 (81.8%)**	**4 (18.2%)**	<0.001
Number of deficits, median (IQR)	**2.0 (1.0-3.0)**	**1.0 (0-1.0)**	0.004
hsCRP, median (IQR)/n, mg/L	13.3 (3.3-54.3)	6.9 (3.1-45.4)	0.82
ESR, median (IQR)/n, mm/h	28 (12.0-49.0)	21 (9.5-26.5)	0.079

Frequency of Abnormal Pituitary Imaging Categories

Imaging abnormality	Number of subjects
Thickened pituitary stalk	15 (24.6%)
Abnormal morphology	11 (18.0%)
Small pituitary	9 (14.8%)
Stalk deviation	7 (11.5%)
Pituitary encasement	3 (4.9%)
Empty sella	
Complete	3 (4.9%)
Partial	4 (6.6%)
Microadenoma	1 (1.6%)
Pars Intermedia cyst (normal variant)	3 (4.9%)
Rathke's cyst (normal variant)	1 (1.6%)



Small size Pituitary

Suprasellar
Post Chiasmatic
Mass

Pituitary Stalk
Thickening

Summary of Findings

1. High frequency of abnormal pituitary imaging in patients with ECD

2. API patients had a higher number of pituitary deficits than those with normal imaging

3. We also noted higher rates of DI and panhypopituitarism in those with API

4. Our results also suggest that API was associated with a younger age, a higher number of pituitary endocrinopathies and ↑DI

Conclusion 1: ↑Abnormal Pituitary Imaging in ECD

- Community estimates of the frequency of API, most commonly involving pituitary adenomas, range from 9.3–11%
- 10.8% prevalence of incidental pituitary imaging abnormalities<< our ECD cohort (47.5%)

- Loss of the posterior bright spot, thickened stalk, and abnormal enhancement are common

- Our study compared to *Courtillot* et al. 2016
  - A higher percentage of stalk thickening (24.6% vs. 13.1%)
  - Also found a higher frequency of pituitary imaging abnormalities (47.5% vs. 24.4%)
  - Like them, loss of the posterior pituitary bright spot in T1 imaging was the commonest API

**Famini* et al. 2011; *#Courtillot* et al. 2016

Conclusion 2: CNS Involvement Related to Poor Outcomes

- CNS involvement is an independent, poor prognostic factor for mortality in ECD subjects*
- Central nervous system involvement in ECD: major cause of morbidity and mortality*
  - abnormal pituitary imaging is a CNS manifestation of ECD

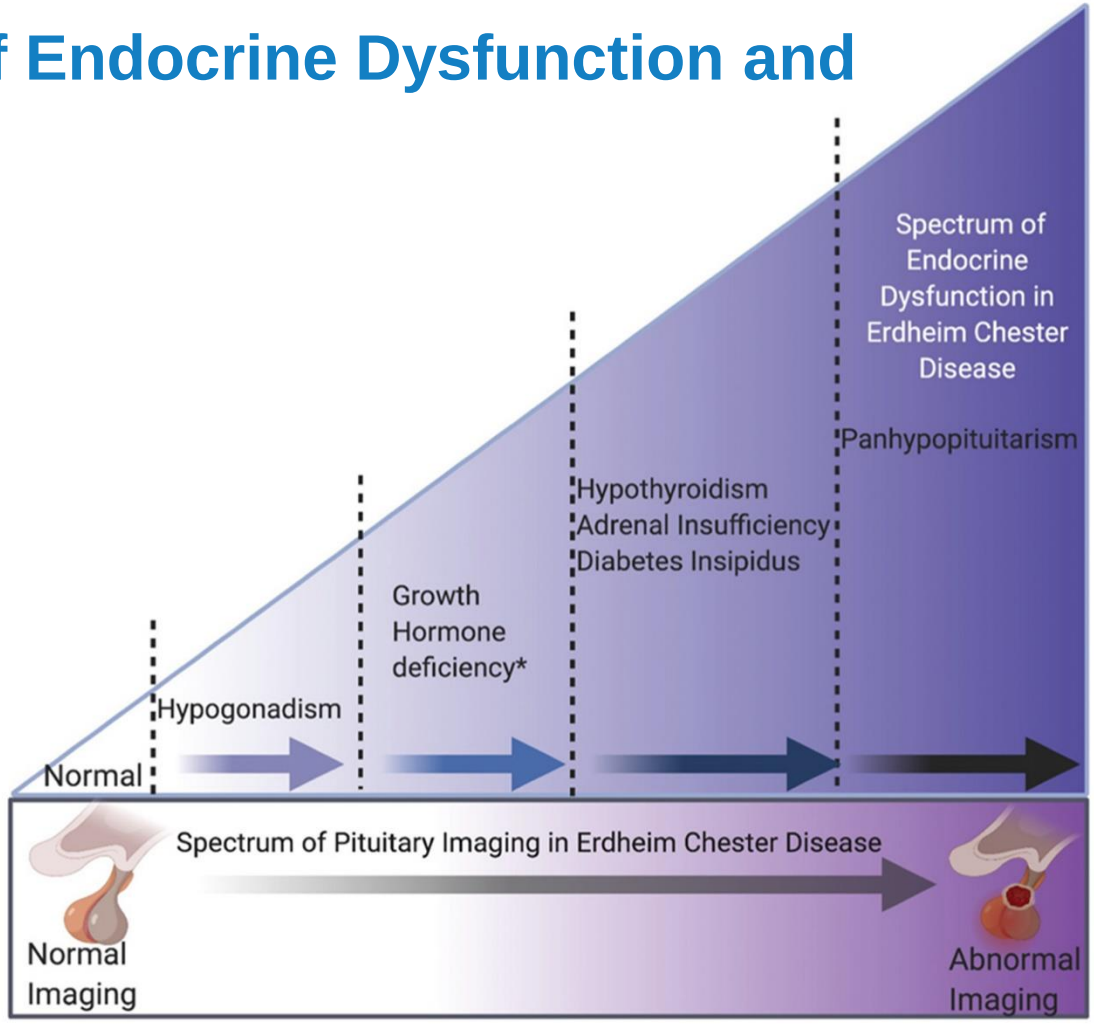
- ECD must be considered in patients with inflammatory, infectious or neoplastic-appearing white matter lesions

- ECD subjects must undergo comprehensive endocrine evaluation and be appropriately treated

- Biochemical testing should be accompanied by a baseline enhanced pituitary MRI (primary diagnostic modality) followed by serial scans as clinically indicated

*Arnaud et al. Blood 2011

Spectrum of Endocrine Dysfunction and API in ECD



* Speculative

Shekhar et al. 2021

Take Home Points

1. There is a high burden of abnormal pituitary imaging in ECD
2. Patients with API are younger than those with normal pituitary imaging
3. There is a higher burden of endocrine disorders in patients with ECD with API
4. Specifically, DI and panhypopituitarism are more common in ECD patients with API compared to those with normal pituitary imaging
5. All ECD patients should undergo pituitary imaging and baseline endocrine evaluation with appropriate follow-up and referral

THANK YOU

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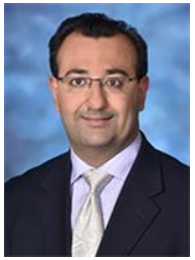

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