Hypothyroidism in Erdheim-Chester Disease: Experience from the National Institutes of Health

Skand Shekhar MD*

Clinical Fellow, Adult Endocrinology

NICHD, National Institutes of Health, Bethesda MD

Fady Hannah-Shmouni, MD, FRCPC

Associate Investigator, Stratakis Lab, SEGEN, NICHD, NIH

William A Gahl MD PhD, Juvianee I. Estrada-Veras MD, and Kevin O'Brien MS-CRNP

*First co-authors

Disclosures

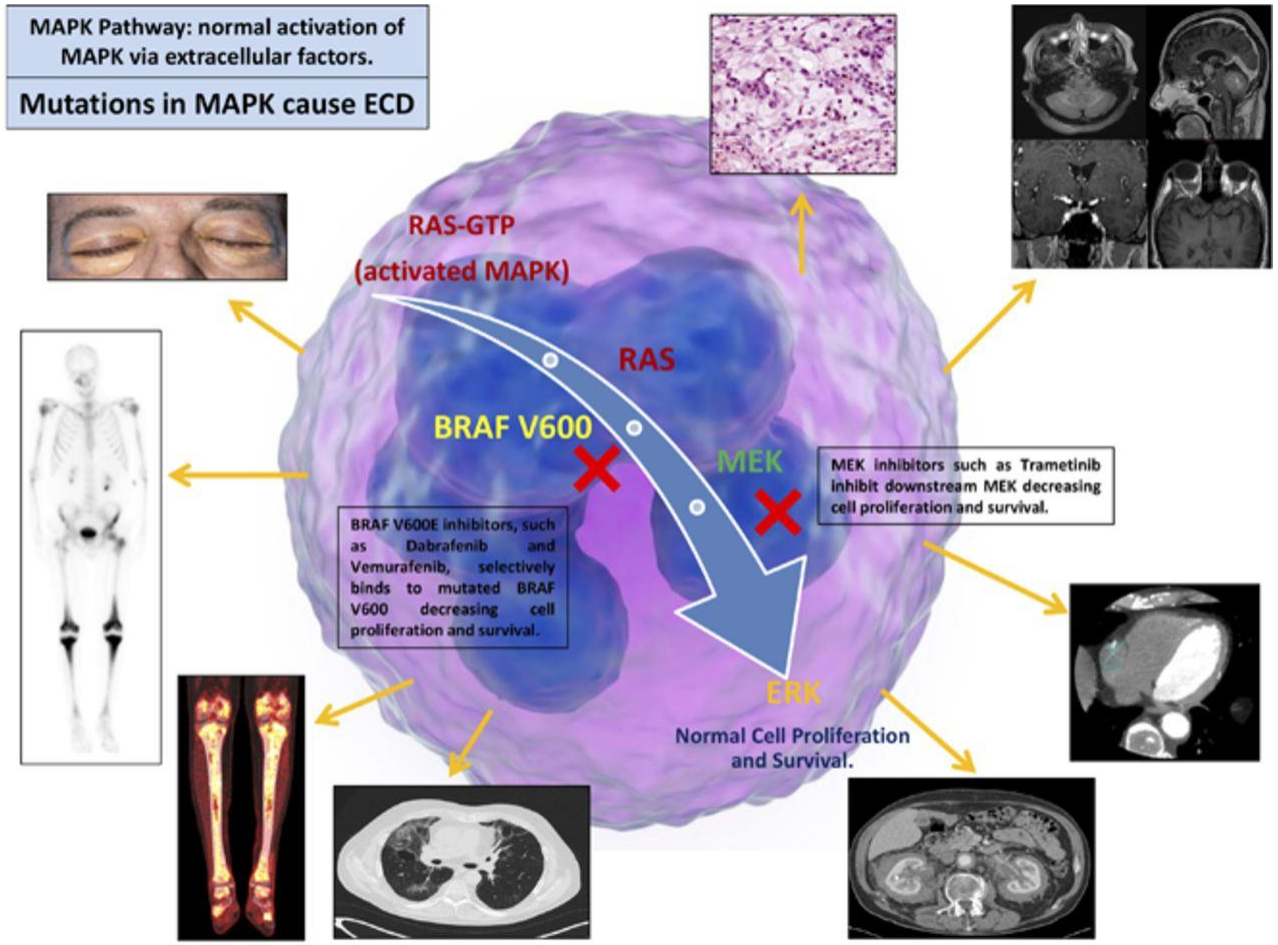
- Nothing to disclose

Erdheim-Chester disease (ECD)

- Hematopoietic neoplasm of histiocytic origin, first described by Jakob Erdheim and William Chester in 1930
- Characterized by the accumulation of foamy macrophages, chronic inflammation, fibrosis, and organ failure (60% mortality at 3 years from dx)
- Mean age 55 yrs, Male 70%

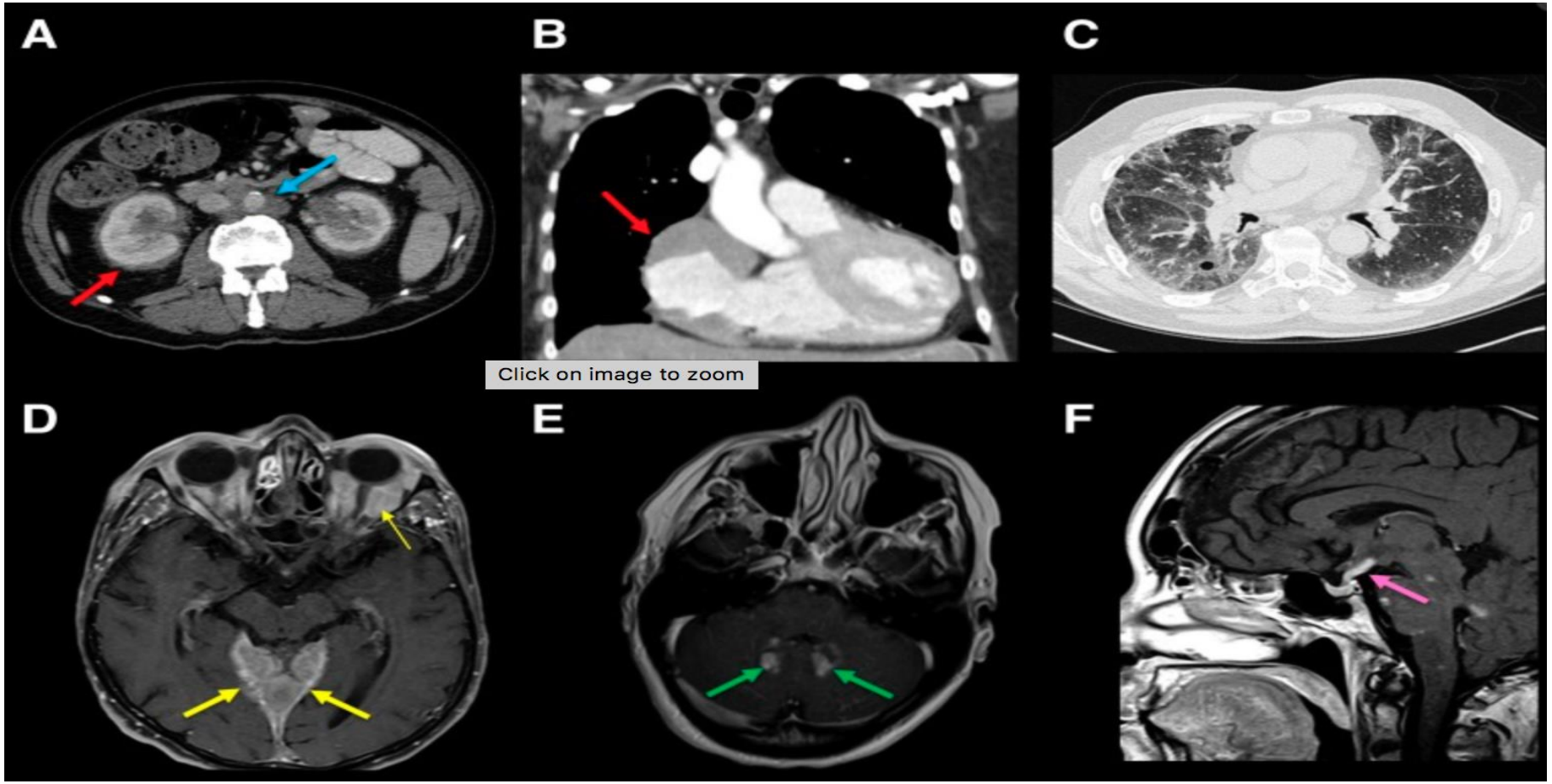
Diamond EL et al. *Blood* 2014.

Pathogenesis



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

Commonly affected organ systems



Diamond EL. *Blood* 2014.

Objectives

- To describe the clinical, radiographic, and biochemical findings from patients with ECD and with or without hypothyroidism

Hypothyroidism

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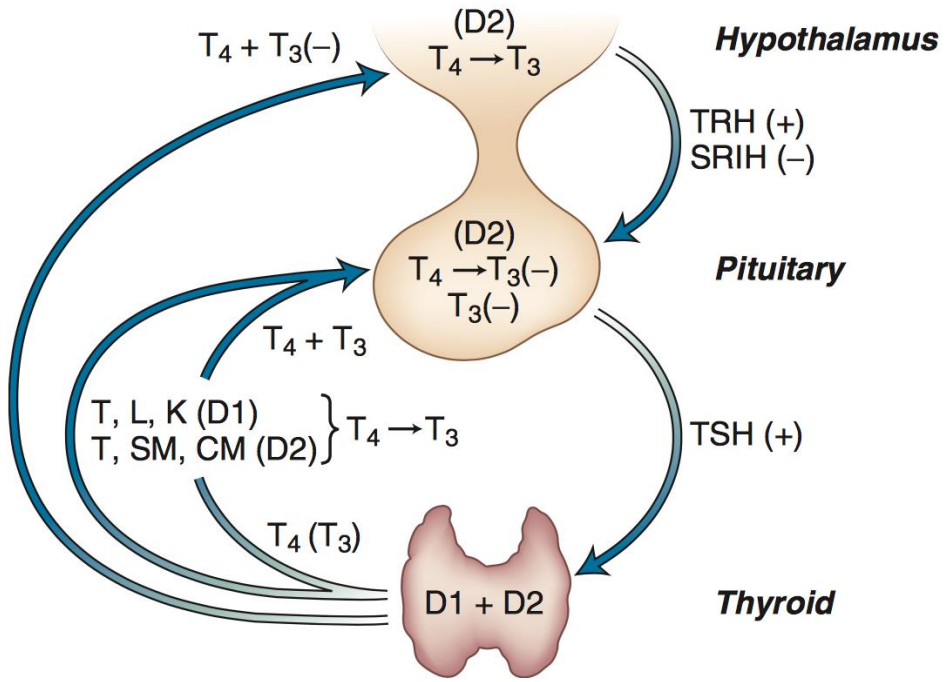


Picture Courtesy: Williams Textbook of Endocrinology. Philadelphia, Pennsylvania : Elsevier. 2016. 13th ed

Hypothyroidism

Types of Hypothyroidism	Definitions
Primary Hypothyroidism	Biochemical diagnosis: TSH > RR (0.27-4.2 mIU/ml) with free thyroxine (fT4) < RR (0.9-1.7 ng/dl) on x2 repeated tests or TSH within RR on LT4
Subclinical Hypothyroidism	TSH > RR with normal fT4 x2
Overt hypothyroidism	TSH > RR and fT4 < RR with symptoms
Central hypothyroidism	fT4 < RR or low-normal levels in conjunction with a low, normal, or mildly elevated TSH

RR: reference range
LT4: levothyroxine therapy

ECD protocol

- Clinical and Pathophysiological Investigations into Erdheim-Chester Disease (11-HG-0207)
- Natural history study designed to better understand and describe the natural history, pathophysiology, and response to therapy
- Prospective design to enroll and follow qualified men and women, of all ethnic groups, ages 2 to 80 years, who were screened for candidacy prior to enrollment
- The NIH Clinical Center - the only center
- Follow up every 2-3 years

Methods

- A prospective cohort study of biopsy-confirmed cases of ECD was conducted at the National Institutes of Health, Bethesda, Maryland
- We retrospectively reviewed records of sixty-one subjects
- Clinical, radiographic, and biochemical characteristics were assessed for all ECD patients

Methods

- All subjects underwent baseline evaluation with a thyroid function test, including TSH, free thyroxine (fT4) and total thyroxine (T4)
- Those already on levothyroxine supplementation were inferred to have hypothyroidism. Their previous records were reviewed and they were interviewed to subclassify the category of hypothyroidism (primary vs. central)
- Subjects suspected to have central hypothyroidism underwent TRH stimulation test

Results

Baseline characteristics	Value
Age	54.3 ± 10.8 years
Sex	46 males (75%)
Mean time to diagnosis	4.2 years
Hypothyroidism- total	17 patients (28%)
Mean TSH (mcIU/mL)	2.00 ±1.63 (0.27-4.20)
Mean free T4(ng/dL)	1.52 ±1.51 (0.9-1.7)

Results

- The prevalence of hypothyroidism was higher than general population estimates (28% vs. 3.7%, $P<0.05$)
- No subject presented with myxedema coma or thyrotoxicosis
- Twelve patients had primary hypothyroidism
- Five patients had biochemical findings or history suggestive of central hypothyroidism (CH)
- Out of 5 patients suspected to have CH, one underwent additional dynamic testing

Isolated Central Hypothyroidism

- 61-year-old Caucasian female with ECD
- Complications of ECD:
  - cerebellar dysfunction
  - retroperitoneal fibrosis
  - osteosclerosis
- Genetics: *BRAF* V600E pathogenic variant
- Biochemical pattern suggestive of isolated central hypothyroidism

Isolated Central Hypothyroidism

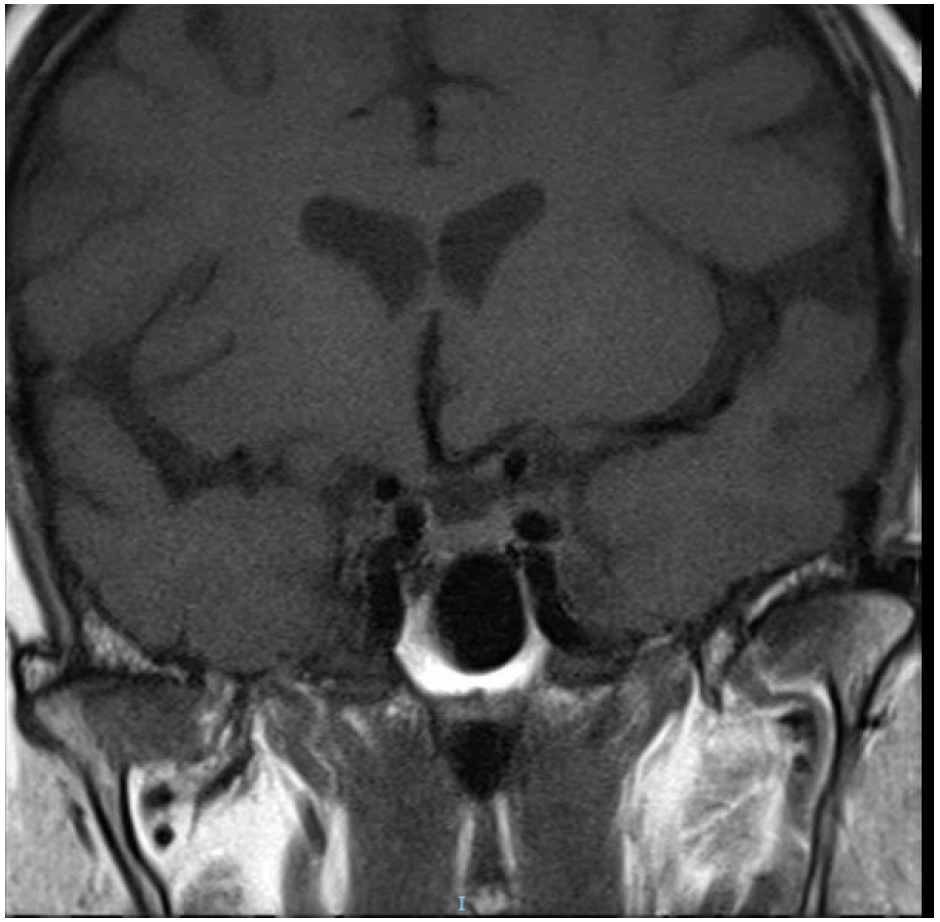
- She did not report symptoms suggestive of clinical thyroid disease
- Physical examination was unremarkable

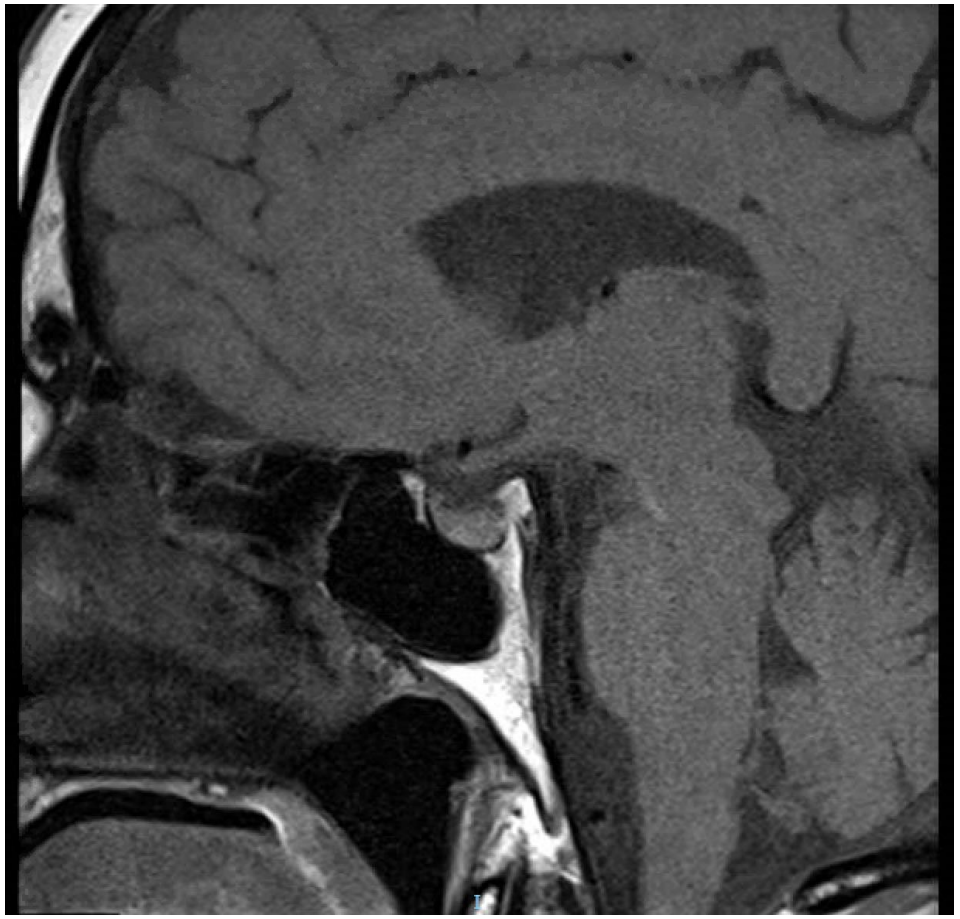
Isolated Central Hypothyroidism

- TSH 0.16 mcIU/mL (nl: 0.27-4.20)
- fT4 1.2 ng/dL (nl: 0.9-1.7)
- normal baseline pituitary function test

- Pituitary MRI showed a small hypoenhancing lesion in the posterior aspect of the pituitary gland that was clinically insignificant

Pituitary Imaging





TRH stimulation test

- A gold standard test currently not available in the United States
- Principle: Hypothalamus releases TSH releasing hormone that stimulates the secretion of TSH from anterior pituitary in normal individuals
- The normal increment in TSH at 20 minutes is 5 to 30 mU/L, with a subsequent decrease at 60 minutes
- Utility: A normal rise of TSH with TRH administration rules out central hypothyroidism

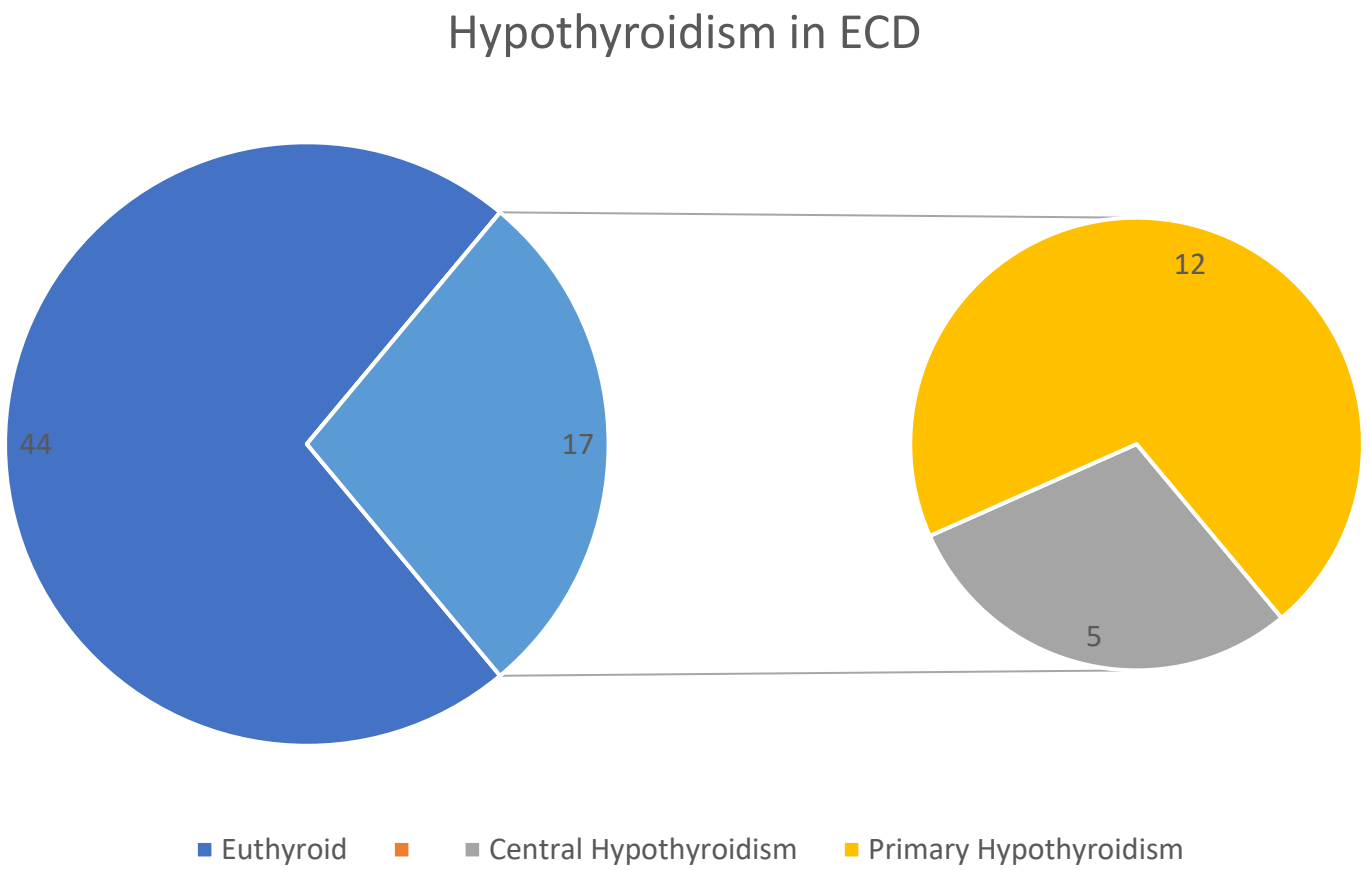
- Dynamic TSH-secretion testing with a thyrotropin releasing hormone (200 µg IV synthetic TRH with serial TSH testing) with blood draws every 15 minutes starting 15minutes before the injection

Time	TSH value (mcIU/mL)
-15 minutes	0.35
0 minutes (TRH injected)	0.33
15 minutes	1.30
30 minutes	2.00
45 minutes	1.12
60 minutes	1.33
75 minutes	1.81
90 minutes	2.90

TRH stimulation test

Conclusion: blunted response consistent with central hypothyroidism; baseline TSH 0.35 mcIU/mL, peak 2.90 mcIU/mL (ΔTSH <7 mcIU/mL).

Results


Hypothyroidism in ECD
44
17
12
5
Euthyroid
Central Hypothyroidism
Primary Hypothyroidism

Results

- Seventeen subjects were on levothyroxine replacement
- Seven subjects suspected of primary hypothyroidism underwent TPO testing, out of which 4 had positive antibodies
- 3 subjects had primary hypothyroidism of unclear etiology with negative TPO
- The antibody status of 4 subjects suspected to have primary hypothyroidism was unknown
- Five subjects had a history or testing suggestive of central hypothyroidism
- One subject had total thyroidectomy for a benign tumor with mechanical symptoms

Results

- The noted proportion of CH in our cohort of ECD hypothyroid subjects was much higher (29.4%, $P<0.05$) than the community (CH accounts for about one of 1,000 hypothyroid patients in the general population)
- The prevalence of central hypothyroidism was 8.1% in our ECD cohort as opposed to 1:20,000 to 1:80,000 in the general population
- 47.05% (8/17) patients with hypothyroidism had a confirmed *BRAF V600E mutation*. One patient out of 17 didn't undergo testing.

Conclusions

- Our cohort demonstrated a statistically significant higher incidence of hypothyroidism compared to general population
- The incidence of CH is significantly higher than the general population and similar to previously reported rates, 9.5%
- The etiology of primary hypothyroidism in ECD is yet to be determined
- Every patient with ECD needs to be evaluated for hypothyroidism with a full thyroid function test (TSH, fT4, TT4, TT3, TPO)

C. Courtillot S. et al. Endocrine Manifestations in a Monocentric Cohort of 64 Patients With Erdheim-Chester Disease. JCEM, Volume 101, Issue 1, 1 January 2016, Pages 305–313

Limitations

- Selection criteria for hypothyroidism was based on historical records
- Dynamic testing or antibody testing was not performed in all patients with hypothyroidism
- Thyroid imaging was not performed in all subjects

Thank You

- The authors appreciate the cooperation of the ECD patients and of the Erdheim-Chester Disease Global Alliance

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- All authors have nothing to disclose