



A SYSTEMATIC APPROACH TO MEDICALLY
UNEXPLAINED SYMPTOMS

APPROACH TO THE PATIENT WITH “ADRENAL FATIGUE”

Neena Natt MD

August 17-20, 2022
The Ritz-Carlton, Half Moon Bay

[@MayoClinicGIM](https://twitter.com/MayoClinicGIM)



Disclosures

Relevant Financial Relationships

None

Off-Label and/or Investigational Uses

None

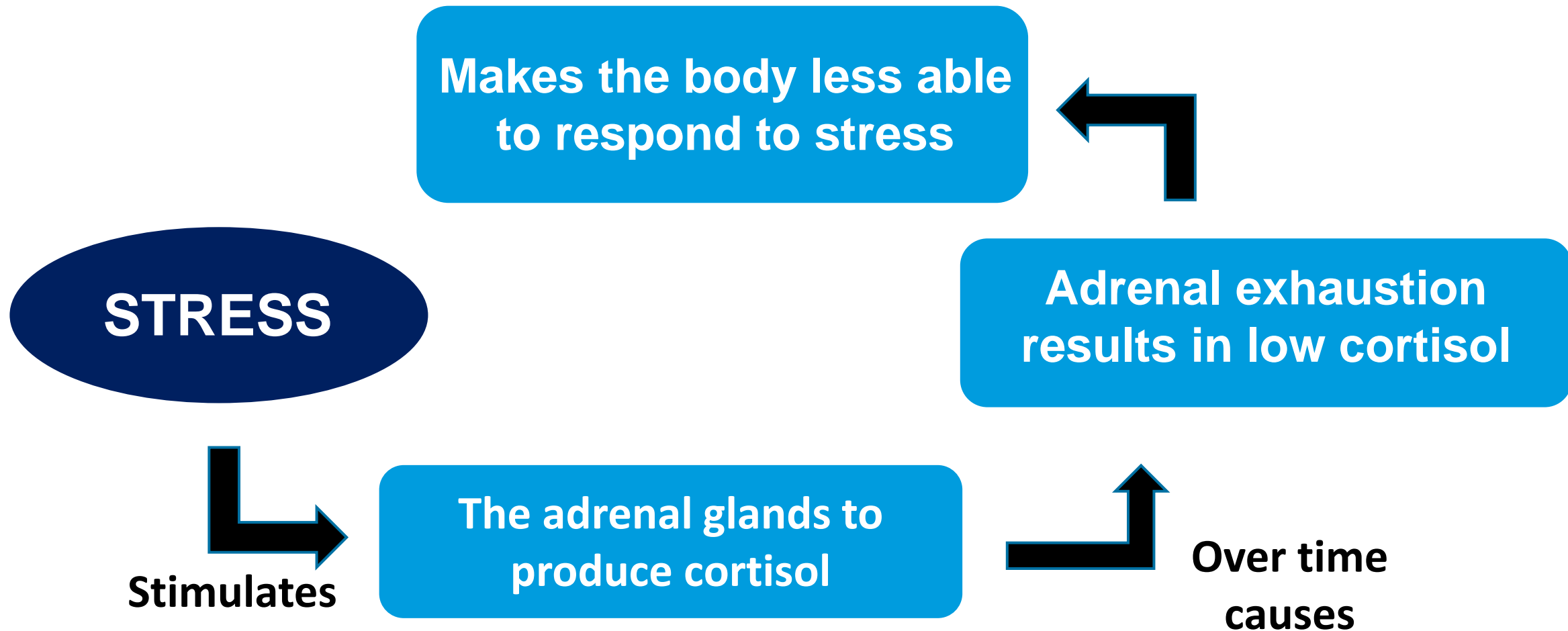
Learning Objectives

- Review what patients are hearing about “adrenal fatigue” – cause, symptoms, and treatment
- Recommend a practical approach to the evaluation and management of the patient who present with a diagnosis of “adrenal fatigue”
- Distinguish true adrenal insufficiency from “adrenal fatigue”
 - Pitfalls in test interpretation
 - Role of DHEAS

Review What Patients Are Hearing About “Adrenal Fatigue”

Cause, Symptoms, and Treatment

What are patients being told about the cause of “adrenal fatigue”?



What Are Patients Being Told Are The Symptoms of Adrenal Fatigue?

- *Fatigue*
- *Brain fog*
- *Difficulty waking up*
- *Irritability*
- *Decreased ability to handle stress*
- *Sick more often*
- *Cravings for salty and sweet foods*
- *Need for caffeine to get through the day*

Adrenal Fatigue: How Are Patients Being Diagnosed And Treated?

Diagnosis

- Adrenal fatigue questionnaire
- Salivary cortisol profiles – morning, noon, evening, bedtime (can be bought on the internet to perform at home)

Treatment

- Lifestyle changes
- Herbal supplements – optimizer, power, builder, support, health, relief
- Animal-derived adrenal gland extract
- Hydrocortisone

Some Over-the-counter “Adrenal Support” Supplements Contain Thyroid And Steroid-based Adrenal Hormones

- Measured thyroid and adrenal-based hormones in 12 OTC dietary supplements marketed for “adrenal fatigue support or health”
 - 6 were labeled as “herbal”, others bovine-based or combination bovine-herbal
- All contained detectable amount of T3
- 6 contained adrenal-based hormone (2 of these were “herbal”)
- None declared the presence of hormones on the product label ingredient list

Akturk et al. Mayo Clin Proc 93:284-290, 2018

Clinical Point

Herbal supplements may contain glucocorticoid, and if abruptly stopped, may result in an adrenal crisis (because the pituitary gland is “switched off” due to the exogenous glucocorticoid)

@MayoClinicGIM

Scientific Literature

Adrenal Fatigue - Systematic Review

- 58 articles fulfilled criteria
 - 33 studies of healthy people
 - 25 studies of symptomatic people
- Conflicting results derived from most of the studies
- The most appropriate methods to assess the hypothalamic pituitary adrenal axis were not used to evaluate fatigue
- There is no proof or demonstration of the existence of adrenal fatigue

Cadegjani et al. BMC Endocrine Disorders 16:48, 2016

@MayoClinicGIM

Recommend A Practical Approach To The Evaluation And Management of the Patient Who Presents With A Diagnosis of “Adrenal Fatigue”

Case 1: History

37-year old woman

- 3-year history of fatigue (particularly in the morning despite sleeping well), exercise intolerance, headaches, and “foggy thinking”
- Meds: Paroxetine 20 mg daily, levothyroxine 100 mcg daily.
- Seen multiple physicians including Endocrinology, Neurology, Allergy
 - evaluations negative
- Visited a functional medicine provider:
 - diagnosed with “adrenal fatigue” based on symptom questionnaire and salivary cortisol profile

Case 1: Salivary Cortisol Profile

Cortisol Levels	Inside Range	Outside range
Morning		7.5 Low
Noon		4.0 Low
Evening		2.3 Low
Prior to Sleep	1.1	

Clinical Point

Salivary cortisol measurement can be unreliable in labs that lack quality control

Case 1: Test results

Requested evaluation of her adrenal function:

- Morning cortisol 6.7 $\mu\text{g}/\text{dL}$ (7-25 $\mu\text{g}/\text{dL}$)

Question: what would you do next?

- A. Discontinue paroxetine and repeat AM cortisol
- B. Check an ACTH level
- C. Repeat AM cortisol level
- D. Check a 24-hour urine free cortisol level

Case 1: Test Results

- Repeat baseline AM cortisol 13 $\mu\text{g/dL}$ (7-25 $\mu\text{g/dL}$)
- ACTH stimulation test results normal
- ACTH 48 (10-60 pg/mL)

Clinical Point

A low cortisol value is often not due to adrenal insufficiency!

Causes of Hormone Levels Outside The Normal Range

Considerations:

- Physiologic variation
- Assay technical limitations/interfering substances
- Medication effect
- Non-endocrine disease
- Endocrine disease

Pitfalls In Interpretation

Factors That Impact Cortisol Levels

- Diurnal rhythm - cortisol production decreases throughout the day
- Pulsatile secretion – cortisol intermittently drops below the normal range in healthy subjects
- Cirrhosis, nephrotic syndrome
 - low cortisol binding globulin (CBG); hence falsely low total cortisol levels
- Oral estrogen (OCP, Premarin, Estradiol)
 - high CBG: hence false elevation of total cortisol

Clinical Points

Natural pulsatile nature of cortisol secretion can result in cortisol levels below the normal range even in the morning

Disease states associated with altered CBG can lead to falsely high or falsely low total cortisol levels

Free cortisol is not impacted by CBG

Pitfalls In Interpretation

Impact Of Exogenous Glucocorticoid Use On Cortisol Levels

- Inhaled, injected (within last 3 months), topical, and oral (current or recent) will suppress endogenous cortisol production
 - Both hydrocortisone and prednisone are picked up in the assay as cortisol
 - Endogenous cortisol will be appropriately low if patient is taking supraphysiologic doses of glucocorticoid
 - Last dose of hydrocortisone or prednisone should be taken 24 hours before cortisol blood draw

Clinical Point

Exposure to glucocorticoids is a common cause of “falsely” low cortisol levels

Approach To The Patient Who Has Been Told That They Have “Adrenal Fatigue”

History

- Carefully listen to symptoms
- Ask what interventions have been tried, what helped, and by how much
- Ask: “What do you think is going on?”
- Summarize the history and (together with the patient) identify the top 3 concerns

Evaluation

- Suggest a standardized endocrine evaluation
- Discuss pre-test probability of adrenal insufficiency (set expectations)
- Consider symptom-specific evaluation

Potential Causes of Symptoms Thought To Be Due To “Adrenal Fatigue”

- Inadequate sleep or sleep disorder
- Lack of exercise
- Stress
- Mood disorder
- Other medical conditions

“Adrenal Fatigue” Evaluation

Adrenal function

- Baseline AM cortisol
- Baseline ACTH
- ACTH stimulation test

Symptom-specific

- +/- Overnight oximetry/sleep medicine
- +/- Dietician/Nutrition Clinic
- +/- Psychiatry/Behavioral Therapy
- +/- Stress Management

Approach To The Patient Who Has Been Told That They Have “Adrenal Fatigue”

Counseling/Discussion

- Address any erroneous (or correct) interpretations and beliefs
- Explain and provide feedback on any abnormal results and previous work up
- Empathize with the patient and acknowledge the struggle
- Acknowledge that medicine does not have the answer to everything

Distinguish True Adrenal Insufficiency From “Adrenal Fatigue”

Pitfalls In Test Interpretation

***Could Some Patients With Unexplained Symptoms
 (“Adrenal Fatigue”) Actually Have Adrenal
 Insufficiency?***

Case 2: History and labs

27-year old man

- 18-month history of mild symptoms of fatigue, lower appetite, intermittent nausea, legs ached
- Chronic opioid therapy for back pain related to a car accident (2 years ago)
- Transient hyponatremia when hospitalized with pneumonia in previous year

Outside labs: cortisol 7.5 (7-25 $\mu\text{g}/\text{dL}$).

Labs here:

- Morning cortisol 7.2 $\mu\text{g}/\text{dL}$ (7-25 $\mu\text{g}/\text{dl}$)
- Electrolytes, CBC, LFTs, prolactin, TSH and FSH all within the normal range.

Cosyntropin Stimulation Test

Case 1		
Time (minutes)	Cortisol (7-25 µg/dL)	ACTH (10-60 pg/mL)
0	7.1	12
30	10.5	
60	13	

Question: Does this patient have adrenal insufficiency?

- A. Yes – secondary adrenal insufficiency
- B. Yes – primary adrenal insufficiency
- C. No – Cosyntropin stimulation test is normal
- D. I don't know

How To Interpret a Cosyntropin Stimulation Test (CST)

- Normal response - peak cortisol $>18 \mu\text{g/dL}$ – based on older polyclonal antibody assays
 - $1/3$ pts achieve max. response at 30 minutes and $2/3$ at 60 minutes
- Newer monoclonal and LC-MS/MS assays have greater specificity for cortisol
- Recent literature suggests the cut of cortisol value for a positive CST should be 14 to 15 $\mu\text{g/dL}$
 - **However** - Interpretation of CST results should occur in the context of degree of clinical suspicion (pretest probability)
 - sensitivity of the test is suboptimal for the diagnosis of **secondary adrenal insufficiency**

Diagnostic Accuracy of the Cosyntropin Stimulation Test in Secondary Adrenal Insufficiency

Table 1. Meta-Analysis Results: ACTH Stimulation Tests for the Diagnosis of Secondary Adrenal Insufficiency

	Estimate	95% CI
Adult High-Dose ACTH Stimulation Test		
Sensitivity	0.64	0.52–0.73
Specificity	0.93	0.89–0.96
Likelihood ratio for positive test	9.1	5.7–14.6
Likelihood ratio for negative test	0.39	0.30–0.52
Diagnostic odds ratio	23	13–42

- Reasonable LR for + test
- Suboptimal LR for - test
- Test is more helpful in ruling in the condition when +
- Test is less reliable in ruling out the condition when -
- Pretest probability of disease important when interpreting results

Case 2: Diagnosis

Diagnosis: Secondary adrenal insufficiency (opioid therapy)

- Peak ACTH-stimulated cortisol level 13
- ACTH inappropriately within the normal range

- Further Evaluation
 - MRI head negative
 - Other pituitary function intact

DHEAS as a potential diagnostic marker of adrenal insufficiency

- Secretion mediated by ACTH
- Almost exclusively produced by adrenal glands
- Long half life - 20 hours

Mayo clinic retrospective study

- DHEAS of >100 mcg/dl predicts a normal CST with a false negative rate of 3%
- DHEAS of <25 mcg/dl predicts a positive CST with a false positive rate of 9%

Suresh et al. J Endocrine Soc 2021:5 (suppl 1)

Clinical Points

Adrenal insufficiency is very unlikely if DHEA-s levels are normal

A low DHEAS by itself is not diagnostic of adrenal insufficiency

A baseline cortisol and DHEAS may be used as first line tests to evaluate for adrenal insufficiency and potentially avoid the need for a CST

@MayoClinicGIM

Case 2: Treatment and Outcome

- Hydrocortisone therapy started
 - Within a few days - felt much better, more energy, no nausea, appetite better, no leg aches.

Clinical Point

Chronic adrenal insufficiency can be present even when cortisol levels are in the low normal range - adrenal insufficiency less likely if baseline cortisol ≥ 10 ($\mu\text{g/dL}$)

Chronic opioid use may result in secondary adrenal insufficiency

An underrecognized cause of adrenal insufficiency

- Adrenal insufficiency can occur with a wide range of opioids - fentanyl, oxycodone, tramadol, methadone, heroin
 - Estimated prevalence 9 to 29%
 - Time to onset – weeks(?) to months
- Risk factors for development of adrenal insufficiency currently not identified
- The time to recovery or the lowest opioid dose at which the hypothalamic-pituitary axis recovers is unknown.

FDA Safety Communication 2016

- Required new statement about adrenal insufficiency added to the *Warnings and Precautions* section of all opioid labels.
- Suggestions:
 - Perform diagnostic testing if adrenal insufficiency is suspected.
 - Treat with glucocorticoid if adrenal insufficiency confirmed
 - Wean opioids, if appropriate.
 - Perform follow-up assessment of adrenal function if opioids discontinued.

Traumatic Brain Injury (TBI)

An Under Recognized Cause Of Adrenal Insufficiency

Systematic Review

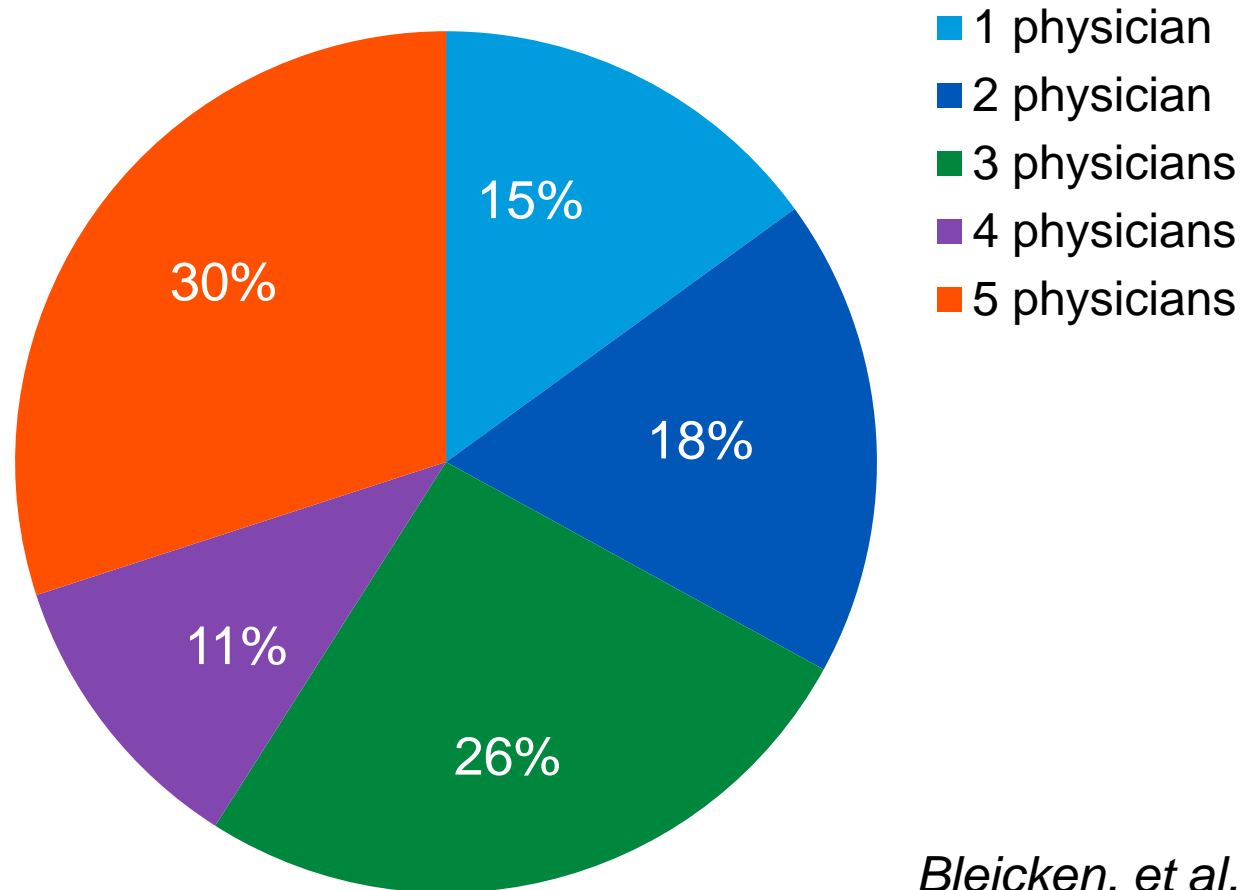
- 1203 TBI patients
- 6% prevalence of adrenal insufficiency one year post-TBI

Tanrivedi et al. Endocrine Reviews 36:305-342, 2015

@MayoClinicGIM

Delayed Diagnosis Of Adrenal Insufficiency

Number Of Different Physicians Seen By Patients With Chronic Adrenal Insufficiency Because Of Her/His Symptoms Before Correct Diagnosis Given



Common symptoms

- All - fatigue/lassitude
- Most - anorexia, nausea
- Many - limb discomfort

Bleicken, et al. Am J Med Sciences. 339(6):525-531, 2010

Summary

- Adrenal fatigue has not been verified as a disease
- The symptoms attributed to adrenal fatigue are likely due to multifactorial causes:
 - poor sleep, poor diet, stress, inactivity, mood disorders
 - or other health problems
- Supplements and vitamins used to “treat” adrenal fatigue may not be safe
 - Herbal” supplements may contain glucocorticoid
 - Taking supplements that contain adrenal extract may cause secondary adrenal insufficiency (and adrenal crisis when stopped)

Summary

- True chronic adrenal insufficiency can go unrecognized for years
 - non-specific symptoms of fatigue, nausea/loss of appetite, myalgia and/or arthralgia
- AM cortisol Levels ≥ 10 $\mu\text{g/dL}$ indicate adequate basal cortisol production in most patients
- Pulsatility, exogenous glucocorticoids and abnormalities in CBG can lead to falsely low or high total cortisol levels
- Adrenal insufficiency is very unlikely if DHEAS is normal
- Perform a CST stimulation test when:
 - AM cortisol is low (or < 10) and symptoms suggestive of adrenal insufficiency
 - or if low suspicion for adrenal insufficiency, but AM cortisol is low on 2 occasions
- Interpretation of CST should occur in **context of degree of suspicion for disease** (lower cortisol cut off level with newer assays)

QUESTIONS & ANSWERS

