Practical Strategies for Management of the Pseudo-Endocrine Patient (May 26, 2016)

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Learning Objectives
1. Discuss non-specific symptoms that may occur in many Endocrine disorders as well as non-endocrine conditions and in some people without any identifiable disease.
2. Review diagnostic testing for common endocrine conditions and the limitations of these tests to completely evaluate all aspects of potential endocrine pathophysiology.
3. Develop a practical approach to the evaluation and management of patients with pseudo-endocrine disorders.

Case 1
A 32 year old woman has been experiencing fatigue, depression and difficulty losing weight for 2 years. Thyroid tests ordered online have been normal except a moderately low reverse T3. She has read that thyroid tests don’t accurately evaluate thyroid function and requests thorough thyroid testing and treatment.

PMH: Negative
Meds: Multiple supplements
PE: BP 122/84  P 80  Ht 5’6”  Wt 172 lb.
   Complete exam normal
Lab Report:  
  TSH 1.2 mU/L (nl: 0.45-4.5) 
  Free T4 1.3 ng/dl (nl: 0.8-1.8) 
  Free T3 3.1 pg/ml (nl: 2.3-4.2) 
  Reverse T3 9 ng/dl (nl: 10-24)

Possible Interpretations:
- Symptoms are not related to the thyroid
- Hypothalamic-Pituitary disease is the problem
- TSH level is not in the optimal range
- There is a coexisting autoimmune disease
- Hashimoto’s Disease itself causes symptoms
- Maybe we should consider other possibilities

Questions:
Do we really know that nothing is wrong with the entire hypothalamic pituitary thyroid axis? Are we sure that our current tests evaluate this axis completely?

Comments:
Hypothyroidism most often develops as a result of thyroid disease (primary hypothyroidism) but can also occur from disorders of the pituitary gland or hypothalamus (central hypothyroidism). Overt primary hypothyroidism is diagnosed by finding elevated serum TSH levels associated with decreased serum FT4 levels. Mild hypothyroidism (also called subclinical hypothyroidism) is diagnosed when serum TSH levels are elevated but FT4 levels are within the reference range. Central hypothyroidism is characterized by low (sometimes low normal) serum FT4 levels in
association with TSH levels that are low, normal or slightly elevated. Primary hypothyroidism is most often due to autoimmune lymphocytic thyroiditis, surgery or radiation therapy.

Hypothalamic-pituitary-thyroid axis physiology is highly complex, involving hypothalamic and pituitary regulation of thyroid hormone (TH) secretion from the thyroid gland, TH transport by proteins in the bloodstream, TH uptake across cellular and nuclear membranes into target cells, TH binding to nuclear receptors, TH regulation of transcription machinery to activate or suppress target genes, translation of mRNA into thyroid regulated proteins and subsequent actions of those TH regulated proteins. It is possible that symptoms could result from inherited or acquired abnormalities at any of these multiple steps of TH physiology for which we currently do not have adequate tests. Alternatively, symptoms could also result from the inflammation in the thyroid or from coexisting autoimmune diseases. Recognition of these possibilities and the development of compassionate and supportive relationships with these patients are usually beneficial.

Discussion with Patient:
Honesty. “I’m not sure what is causing your symptoms. I have done all the appropriate tests and have not found an Endocrine disorder.”
Encouragement. “While we didn’t find a cause for your symptoms, your test results do indicate that you do not have any serious conditions.”
Compassion. “I hope that your symptoms will resolve soon with healthy lifestyle measures. I am certainly willing to repeat some of your tests in 3-6 months if the symptoms persist.”

Recommendations:
Good Sleep Habits
Regular Exercise
Good Nutrition
Stress Reduction
Depression Management
Treatment of Co-existing Illnesses

- Thyroid Support Supplements – No Proven Benefit
- Thyroid Hormone Replacement – No Proven Benefit Unless Hypothyroidism Verified

Case 2
A 47 year old woman has been experiencing fatigue for about 15 years but complains of “total exhaustion” progressively over the past year. She does not sleep well but does not snore. Appetite is poor. Mild weight gain (5 lb) has occurred in the past year. Cannot exercise due to fatigue. She requests to be treated for Adrenal Fatigue for which she has tested positive.
PMH: Mononucleosis at age 18  Meds: Occasional prescription pain medication
PE: BP 128/70  P 80  Ht 5’8”  Wt 157 lb. (Orthostatic vitals negative)
Complete exam normal
Lab: Full Day Salivary Cortisol Profile – Adrenal Fatigue

Questions:
Do we really know that nothing is wrong with the entire hypothalamic pituitary adrenal axis?
Are we sure that our current tests evaluate this axis completely?
**Comments:**
Adrenal insufficiency can develop as a result of adrenal disease (primary adrenal insufficiency) or from disorders of the pituitary gland or hypothalamus (secondary adrenal insufficiency). Current guidelines state that the best screening test for adrenal insufficiency is a morning serum cortisol level between 8 and 9 AM. A serum cortisol level less than 3 mcg/dL is diagnostic of adrenal insufficiency, whereas a serum cortisol level greater than 15 mcg/dL rules out adrenal insufficiency; an ACTH stimulation test should be performed in patients whose morning cortisol level is between 3 and 15 mcg/dL. The ACTH stimulation test, however, has some limitations, particularly in patients with secondary adrenal insufficiency.

Hypothalamic-pituitary-adrenal axis physiology is also complex, involving hypothalamic and pituitary regulation of cortisol secretion from the adrenal glands, cortisol transport by proteins in the bloodstream, cortisol uptake across cellular and nuclear membranes into target cells, cortisol binding to nuclear receptors, cortisol regulation of transcription machinery to activate or suppress target genes, translation of mRNA into cortisol regulated proteins and subsequent actions of those cortisol regulated proteins. It is possible that symptoms could result from inherited or acquired abnormalities at any of these multiple sites of cortisol physiology for which we currently do not have adequate tests. Recognition of this and the development of compassionate and supportive relationships with these patients are usually beneficial.

**Discussion with Patient:**
Honesty
Encouragement
Compassion

**Recommendations:**
Good Sleep Habits
Regular Exercise
Good Nutrition
Stress Reduction
Depression Management
Treatment of Co-existing Illnesses

- Adrenal Support Supplements – No Proven Benefit
- Adrenal Replacement Therapy – Avoid Unless Adrenal Insufficiency Verified

**Case 3**
A 53 year old man muscle weakness, exercise intolerance, fatigue, lack of motivation, increased need for sleep, and difficulty concentrating for about 5 years following a MVA with “whiplash injury”. He read about post-traumatic hypopituitarism and has had online tests done. Thyroid and adrenal tests were normal but his GH level was low and his IGF-1 level was low normal. He requests treatment for Growth Hormone Deficiency.

**PMH:** GERD, Colon Polyps  **Meds:** None
**PE:** BP 140/85  P 76  Ht 5’11”  Wt 208 lb.
  Complete exam normal
Lab: Growth Hormone 0.05 ng/ml (nl: 0.05-3.0)  
IGF-1 82 ng/ml (nl: 60-220)

Questions:  
Do we really know that nothing is wrong with the entire hypothalamic pituitary GH/IGF-1 axis?  
Are we sure that our current tests evaluate this axis completely?

Comments:  
Growth Hormone Deficiency in adults most often develops as a result of tumors, inflammation, infection, trauma, surgery, or radiation therapy involving the hypothalamus or pituitary gland. The diagnosis of GH deficiency can be made in the presence of a low serum IGF-I level in a patient with known hypothalamic or pituitary disease and documented deficiency of 3 other pituitary hormones. Otherwise, GH stimulation testing with the GHRH/arginine stimulation test, insulin tolerance test or glucagon stimulation test can be performed.

Hypothalamic-pituitary-hepatic GH/IGF-1 axis physiology is also complex, involving hypothalamic and pituitary regulation of GH secretion, GH transport in the bloodstream, GH binding to GH receptors, especially in the liver, and initiating second messenger signaling to stimulate hepatic IGF-I secretion, IGF-I transport by proteins in the bloodstream, IGF-I binding to IGF-I receptors on target tissues, and initiation of second messenger signals in target tissues. It is possible some symptoms could result from inherited or acquired abnormalities at any of these multiple steps of GH/IGF-1 physiology for which we currently do not have adequate tests. Recognition of these possibilities and the development of compassionate and supportive relationships with these patients is usually beneficial.

Discussion with Patient:  
Honesty  
Encouragement  
Compassion

Recommendations:  
Good Sleep Habits  
Regular Exercise  
Good Nutrition  
Stress Reduction  
Depression Management  
Treatment of Co-existing Illnesses

- GH Secretagogues – No Proven Benefit  
- HGH Therapy – Avoid Unless GH Deficiency Verified

Final Considerations:  
What the Patient Says: Fix my thyroid, adrenal, or pituitary condition  
What the Patient Means: Please Help Me!  
The Patient’s Quality of Life is Poor And He/She is Frustrated  
It’s an Honor that She/He Entrusts You With an Opportunity to Help Her/Him
Furthermore:
We don’t know what we don’t know.
We are not really sure there is not an endocrine condition that is very subtle or for which we don’t even have a test.

**Final Recommendations:**
- Listen attentively
- Examine your patient
- Offer additional testing, if appropriate
- Admit that current testing options have some limitations
- Always provide honesty, encouragement and compassion

**Final Thoughts:**
- It’s An Exciting Time to be an Endocrinologist!
- There is So Much Still to Learn.
- And So Many People We May Be Able to Help!

**References**


