CLINICAL VIGNETTE

Endocrinopathies Associated with Anorexia Nervosa: A Case Report and Literature Review

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Case Presentation

A 27-year-old female with anorexia nervosa and secondary amenorrhea presented to endocrinology for evaluation of amenorrhea. She reported 5-years of amenorrhea from age 18-23, potentially due to strenuous physical exercise and food restriction consistent with anorexia nervosa. From age 23-27, her menstrual cycle was irregular, not occurring for months at a time. The patient participated in a 12-month anorexia nervosa treatment program and reported making progress while in the program. At the time of presentation to endocrinology, she had not experienced menstrual bleeding for the past 3 months. She denied having galactorrhea, dry skin, hair loss or changes in bowel habits. Her medication list included lamotrigine, sertraline and trazadone.

Physical exam included blood pressure of 94/63 mmHg and a BMI of 19.69 kg/m^2. Her appearance was unremarkable. Thyroid was symmetric, without masses. She did not exhibit bradycardia, hypothermia, or dry skin.

Amenorrhea labs included negative pregnancy test, and abnormally normal FSH and LH levels in the setting of undetectable estradiol. Prolactin was normal. Thyroid tests included low free T3 of 167 pg/dL (222 - 383 pg/dL), low free T4 of 0.7 ng/dL (0.8 - 1.7 ng/dL), and normal TSH of 0.82 mcIU/mL (0.3 - 4.7 mcIU/mL).

After her initial endocrinology consultation and completion of anorexia nervosa treatment program, additional tests included: ACTH, cortisol, IGF-1, free T4, TSH, FSH, LH, and estradiol. Results showed detectable estradiol levels and an improved T4 level of 0.90 ng/dL. FSH, LH, TSH, ACTH, AM cortisol, and IGF-1 were within normal limits.

MRI of the sella turcica did not demonstrate any abnormalities of the pituitary gland.

Given her history and laboratory and imaging findings, the patient was diagnosed with hypogonadotropic amenorrhea due to eating disorder. As her labs normalized, she was encouraged to continue nutrition rehabilitation.

Discussion

Anorexia nervosa is a condition of severe malnutrition and distorted body image perception that is associated with endocrinopathies including gonadal axis dysregulation, thyroid axis dysregulation, adrenal axis dysregulation, growth hormone (GH) resistance, and osteoporosis, among others. Evaluating and treating patients with anorexia nervosa for endocrinopathies is essential to preventing present and future harm. Prompt treatment and counseling for the eating disorder may reverse some endocrinopathies and associated symptoms related to malnutrition.

Hypothalamic Pituitary Gonadal Axis

In pre-pubertal and post-pubertal females with anorexia nervosa, gonadal axis dysregulation may result in primary and secondary amenorrhea. Patients with anorexia nervosa exhibit disruption in GnRH release, leading to abnormal gonadotropin pulsatility.[1] In these women, LH pulsatility patterns have been shown to revert to pre-pubertal secretion patterns.[2] This results in decreased stimulation for ovulation and ovarian estrogen production. If these patients are able to gain 90% of the predicted weight for height, menses may resume within 1 year.[1]

Men with anorexia nervosa may experience hypothalamic-pituitary-testicular dysregulation, although the manifestations of their gonadal dysregulation may be less obvious than for women, who may observe loss of regular menses. Chronic calorie deficit has been linked to hypogonadism in the form of diminished body hair and testicular size, as well as low total testosterone levels.[3] Studies suggest the severity of gonadal suppression correlates with the degree of calorie deficit.[3]

Hypothalamic Pituitary Thyroid Axis

Thyroid hormone level in patients with anorexia nervosa are similar to those seen in sick euthyroid syndrome. This includes low T3 levels, low/normal T4 levels, and low/normal TSH levels. As in the state of chronic illness, low T3 levels are due to decreased peripheral conversion from T4, as well as increased conversion of T4 to the inactive reverse T3.[1] This is thought to be an adaptation to the low energy state seen with malnutrition. Release of TRH from the hypothalamus may be

impaired, preventing TSH release despite low peripheral T3. Generally, these patients do not have true hypothyroidism and their thyroid tests will normalize with nutritional rehabilitation. However, atrophy of the thyroid gland has been observed in some anorexia nervosa patients compared to age-matched controls.

Hypothalamic Pituitary Adrenal Axis

As chronic starvation induces physiologic stress, individuals with anorexia nervosa experience a constant state of stress leading to hypercortisolemia.[1] This hypercortisolemia differentiates anorexia nervosa-induced endocrinopathies from primary pituitary dysfunction, which also display hypocortisolemia. Increased bursts of cortisol secretion and half-life of the hormone have been implicated as factors leading to an increased cortisol set point in these patients. This is consistent with concurrently observed inappropriately low ACTH levels.[4]

Growth Hormone Axis

Patients with anorexia nervosa may display acquired GH resistance. Increased GH concentration is due to increased basal secretory rate, increased pulsatile amplitude, and increased pulse frequency.[2] Lower-than-normal levels of IGF-1 in the setting of increased GH is thought to be attributable to decreased GH hepatic receptors. The effect of GH resistance may be stunted longitudinal growth, depending on the developmental stage of anorexia nervosa patients.

Bone Metabolism

Bone density may be decreased in patients with anorexia nervosa, through a multitude of pathways including low estrogen levels, elevated cortisol levels and bone formation suppression in the context of malnutrition.[4] Osteopenia and osteoporosis are common in this population, even in relatively young patients. Younger patients with anorexia nervosa may never reach their peak bone mass even with the correction of nutritional deficiency.

This patient demonstrates multiple endocrinopathies seen with anorexia nervosa. Her initial testing showed abnormally normal FSH and LH levels with undetectable estradiol, suggesting hypogonadotropic hypogonadism. With the exclusion of other causes of central hypogonadism, she was diagnosed with functional amenorrhea related to malnutrition. Her pattern of low/normal T4, low T3, and low/normal TSH is that seen in patients with anorexia nervosa and is was similar to that seen in sick euthyroid syndrome. This highlights the importance of a thorough understanding of endocrine changes in patients with anorexia nervosa to prevent harm from hypogonadism and low bone density and also prevent misinterpretation of abnormal labs that reflect the physiologic response to stress, such as those seen with thyroid and cortisol testing.

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