Hypogonadism in the presence hemochromatosis; A male with high testosterone and estradiol, with clinical hypogonadism eventually found to have hereditary hemochromatosis

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Introduction

- Hereditary hemochromatosis (HH) is a genetic disorder characterized by toxic accumulation of iron with subsequent organ damage.
- Classically presents as hyperpigmentation, cirrhosis and diabetes.
- HH can result in hypogonadotropic hypogonadism due to excess iron deposition in the pituitary gland with predilection for the gonadotrophs.
- We present a case of HH diagnosed in a male with signs of clinical hypogonadism but with elevated sex hormone binding globulin (SHBG), total testosterone, estradiol and normal gonadotrophs.

Case

A 49-year-old male presented to Endocrinology with complaints of chronic fatigue, impotence, decreased libido, gynecomastia, small testes, poor body hair, female pattern voice and pain in multiple joints. He does not have children and has never tried.

Past medical history: Insulin dependent diabetes (diagnosed at age 16)
Family history: Diabetes (maternal grandmother)
Social history: 12oz beer three times a week, denies taking androgen supplements

Vitals: BP 126/86, HR 88, BMI 29.8
Physical exam: sparse facial hair, thin upper and lower extremities, and truncal obesity
Studies: (Table 1)
Imaging: A computed tomography scan of the chest, abdomen and pelvis showed a stable 4 mm pulmonary nodule.

	Value
FSH (1.5-12.4 mIU/mL)	8.5 mIU/mL
LH (1.7-8.6 mIU/mL)	5.63 mIU/mL
Total serum testosterone (249-839 ng/dL)	1212 ng/dL
Free testosterone (35-130 pg/mL)	94.7 pg/mL
Estradiol (5.0-42.5 pg/mL)	58.5 pg/mL
SHBG (12-91 nmol/L)	136 nmol/L
B-HCG (0-1.9 mIU/mL)	<0.1 mIU/mL

Ferritin (30-400 ng/mL)	518.7 ng/mL
Iron (45-176 ug/dL)	210 ug/dL
Binding Capacity (250-425 ug/dL)	230 ug/dL
Transferrin Saturation (15-55 %)	91 %
Albumin (3.8-5.0 g/dL)	4.8 g/dL
ALT (10-50 U/L)	27 U/L
AST (10-50 U/L)	22 U/L
Alkaline phosphatase (0-153 U/L)	117 U/L
Prolactin (4.0-15.2 ng/mL)	9.4 ng/mL
TSH (0.27-4.2 uIU/mL)	1.48 uIU/mL
T4 (0.9-1.7 ng/dL)	1.29 ng/dL
AM cortisol (4.8-19.5 ug/dL)	13.2 ug/dL
ACTH (0-46 pg/mL)	15.5 pg/mL
IGF (52-328 ng/mL)	69 ng/mL
IGF binding protein (3.3-6.7 mg/L)	3.0 mg/L
Macrilen stimulation test Baseline GH (<3.0 ng/mL) 30 minutes 45 minutes 60 minutes 90 minutes	 0.1 ng/mL 18.1 ng/mL 30.6 ng/mL 35.8 ng/mL 27.4 ng/mL
HbA1c	8.1
Hepatitis C antibody	Negative
HIV	Non-reactive

Table 1: Laboratory results

Case continued..

Genetic testing:
- Negative for androgen insensitivity syndromes
- Homozygous C28Y mutation of the HFE gene

Treatment: He was started on anastrozole 1mg daily and weekly therapeutic phlebotomy with resolution of feminizing and hypogonadism symptoms, and normalization of SHBG and estradiol concentrations

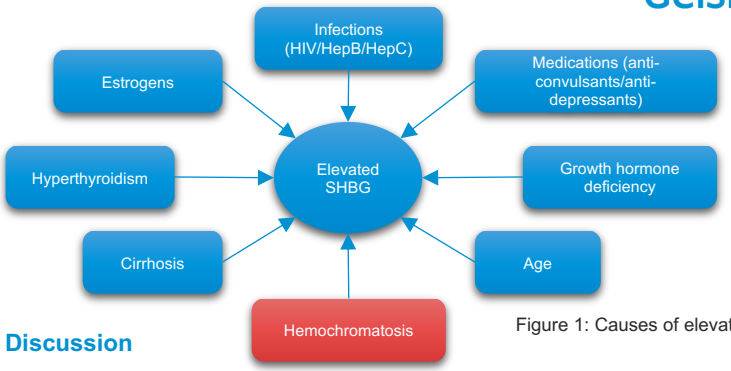

Figure 1: Causes of elevated SHBG

Discussion

- HH has been implicated in hypogonadotropic hypogonadism. However, normal gonadotropins in our patient precludes this.
- There are no well documented association between SHBG in individuals with iron overload that do not have cirrhosis.
- Ferritin is predominantly found in the liver, and the effects of iron overload on SHBG whose synthesis occurs in the liver is largely unclear.
- Excess iron accumulation in the liver may have a direct impact on the level of SHBG
- Inflammation induced by excess iron may increase gene expression related to SHBG or reduce its catabolism. This is further supported by the simultaneous reduction in both ferritin levels and SHBG following 4 weeks of therapeutic phlebotomy. However, the mechanisms of this are yet to be fully established.
- Other causes of elevated SHBG were excluded in this case: hyperthyroidism, liver disease, infections, androgen insensitivity syndromes, GH deficiency and Cushing's syndrome.
- Symptoms of hypogonadism in this patient were likely due to an imbalance between free testosterone and estrogen as a result of elevated SHBG.
- Treatment of hemochromatosis resolved clinical hypogonadism in our patient.

	Pre-treatment (10/21/2020)	On Arimidex alone (12/23/2020)	Post therapeutic phlebotomy + Arimidex (07/20/2021)
Serum Ferritin (30-400 ng/mL)	546.9 ng/mL		352.8 ng/mL
SHBG (12-91 nmol/L)	157 nmol/L		96 nmol/L
Total testosterone (249-839 ng/dL)	1360 ng/dL		1266 ng/dL
Free testosterone (35-130 pg/mL)	94.1 pg/mL		139.4 pg/mL
Estradiol (5.0-42.5 pg/mL	79.2 pg/mL	42.5 pg/mL	26.2 pg/mL

Table 2: Response to treatment

Conclusion

- This case shows that excess iron in hemochromatosis can result in clinical hypogonadism either by causing central hypogonadism or by elevating SHBG (unclear mechanism).
- Elevated SHBG should raise suspicion for hemochromatosis even in the absence of the classic triad once other more common causes have been excluded

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