CLINICAL VIGNETTE

Adult Growth Hormone Deficiency in a Patient with Muscle Wasting Previously Treated for Hypogonadism

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Case Presentation

A 46-year-old male with a 3-year history of decreased muscle bulk and tone and treated with testosterone replacement therapy for two years with no improvement in symptoms presents to endocrine for reassessment. Patient initially presented to his primary care doctor with complaints of fatigue, erectile dysfunction and loss of muscle mass. His initial total testosterone level was 220ng/dl. He was started on testosterone gel 1.62% and titrated up to dose of 4 pumps daily with no significant improvement in his total testosterone or free testosterone levels. Despite high dose testosterone gel, his total testosterone level did not exceed 392ng/dl, and it was concluded that he was not absorbing topical testosterone gel.

Patient was then given testosterone cypionate 200mg intramuscularly every 10-14 days with levels of total testosterone ranging from 626 ng/dl to 1100 ng/dl. Despite improvement in testosterone levels, he continued to have fatigue and inability to maintain his muscle mass. He is an avid marathon runner, who generally competes in at least 3 marathons a year and runs 3-5 miles per day. In the last year, he has not been able to complete even a half marathon and reports dyspnea on exertion with increased muscle fatigue and aching. He presented with a body mass index of 23.5; however, he complains that though his weight has not changed in the last few years, he cannot get rid of his abdominal visceral fat despite his healthy diet and strenuous exercise regimen. He also complained that his memory was "not as good as it used to be" and that at work he had difficulty multi-tasking and concentrating.

On initial physical exam, his blood pressure was well-controlled at 107/73. He was lean but not cachetic and in no apparent distress. He had lean arms and legs with normal strength in his upper and lower extremities and central adiposity. Testicular exam found smaller than expected testicular size and volume but no masses.

Endocrine evaluation included ruling out secondary causes of hypogonadism, which if treated may improve testosterone levels without the use of supplementation. He denied taking opioids, drinking alcohol, using marijuana, or taking herbal supplements that could contain anabolic steroids or natural estrogens. He had a normal sleep study ruling out obstructive sleep apnea, no evidence of hemochromatosis on iron studies, and normal prolactin levels ruling out other possible causes of hypogonadism. He had a normal karyotype ruling out Kleinfelter's. A bone density scan was not approved by his insurance company due to his young age. His 8 AM cortisol level was 20, thus showing no evidence of adrenal insufficiency.

He does have a 10-year history of hypothyroidism, thyroid peroxidase antibody negative, requiring levothyroxine replacement that initially started at 25 mcg daily. Throughout the past 3 years, it has increased to dose of 75 mcg daily. On thyroid ultrasound, he has a normal size gland without nodules.

Given the patient's continued muscle wasting and accumulation of abdominal fat, IgF-1 and growth hormone levels were drawn. Initial IgF-1 was low at 49 ng/ml and repeated two weeks later at 61 ng/ml with normal range for his age group (59-201 ng/ml). He is 5 feet 10 inches tall with his father slightly over 6 feet tall; his mother was 5 feet 5 inches tall. He was always a lean child, and despite being involved in multiple sports in grade school through college, he was never able to increase muscle mass. Both his father and his paternal grandfather had coronary artery disease and suffered myocardial infarctions under the age 50 of years.

An MRI of the pituitary showed a smaller than normal pituitary with concave superior margin with no masses and a normal pituitary stalk without midline shift. Patient denies history of brain trauma.

Due to labs showing lower than expected IGF-1 for his age, glucagon stimulation test was done with 1 mg glucagon administered in the clinic and measurements of growth hormone were taken every 30 minutes for 4 hours. A peak level of 4.5 ng/ml was reached after 2 hours, higher than the

level of < 3.0ng/ml needed for diagnosis of growth hormone deficiency. He did not experience any nausea, vomiting, diaphoresis, or headache during the test.

The patient returned to discuss the borderline results of his testing. He declined to repeat testing given the time involved that would interfere with his job as a school teacher. Currently, there are no recommendations regarding borderline results from the glucagon stimulation testing for growth hormone deficiency. Given his symptoms and his low baseline IgF-1 lower than the expected baseline for his age group, growth hormone replacement was initiated with somatropin. The recommended initial starting dose was 2-5 mcg/kg of body weight. Patient was 73 kg, and he was started on somatropin 300 mcg once daily. Testosterone therapy was continued at a dose of 200 mg IM every 14 days, which maintained his total testosterone levels in the 400-600 ng/dl range.

After 2 months on growth hormone therapy, his IgF-1 rose to 88 ng/ml. His dose was increased again to 0.5mg, and after another 2 months, his growth hormone rose to 100 ng/ml (normal for his age is 59-201 ng/ml). He is now able to complete marathons without significant dyspnea, and though he has not gained weight, he has noticed decline in his abdominal fat and more definition in his arm and leg muscles. He is also able to concentrate and focus more on multiple tasks. Interestingly, his thyroid function also improved after starting growth hormone therapy, and he required less levothyroxine to maintain normal TSH between 1.0-2.5. His dose was reduce to levothyroxine 50 mcg daily shortly after starting growth hormone therapy and has been on same levothyroxine dose for the last 10 months while on growth hormone therapy.

Discussion

Adult growth hormone deficiency (GHD) is often a diagnosis that is not considered initially due to non-specific symptoms such as fatigue, mood liability, and weight gain. It is not uncommon for male patients to be diagnosed with age-related hypogonadism and treated with testosterone therapy with no improvement in muscle mass and strength, mood, or central adiposity. This patient was already on testosterone therapy for two years with serum levels as high as 1100 ng/dl with no impact on symptoms of primarily weakness and inability to maintain muscle mass despite being very athletic. He also had concerns about coronary artery disease since both his father and paternal grandfather had myocardial infarctions at a young age. Untreated adult GHD can lead to increase risk of coronary artery disease, low bone density and fractures, and overall lower quality of life.[1]

Patients with suspected adult GHD should have evaluation of the rest of the pituitary axis for deficiency. In this patient, since he had already been on testosterone therapy, his LH and FSH were already suppressed due to feedback mechanism from testosterone repletion. One can argue he may have had hypogonadtropic hypogonadism initially. His hypothyroidism did not appear to be central hypothyroidism as his TSH was not suppressed. It is interesting, however, that he had a smaller than expected anterior pituitary on MRI, a finding that is noted in some children with growth hormone deficiency. In a study by Hamilton J et al[2] evaluating 20 patients with isolated GHD and 15 with multiple pituitary hormone deficiencies (MPHD) including GHD ages 2 to 17 years old, pituitary abnormalities were common in 80% with isolated GHD and 93% with MPHD.

Common causes for adult growth hormone deficiency are traumatic brain injury and aneurysmal subarachnoid hemorrhage. These events can result in transient GHD, so it is advised to wait 12 months before testing (3).

If a patient has 3 or more pituitary deficiencies lower than expected for age and sex IgF-1, then a GH stimulation test is not required for diagnosis. The gold standard for testing and diagnosis for adult GHD is the insulin tolerance test, but acceptable alternatives include the Arginine-GHRH test and the glucagon test. The Arginine-GHRH test is not readily available, and the insulin tolerance test is recommended to be done in the hospital setting due to risks of hypoglycemia. The glucagon test is a reliable alternative that can be done in the outpatient setting.

The American Association of Clinical Endocrinologists (AACE) Guidelines in 2009[3] for diagnosis include lower than expected IgF-1, documented pituitary deficiencies, as well as symptoms. The patient's goals of therapy as outlined in the AACE Guidelines in 2009 were as follows:

- For age 30-60 years of age, 0.2-0.3 mg/day starting dose;
- Titration at 1-2 month intervals increased dose by 0.1-0.2 mg/day based on clinical response, side effects, and IgF-1 levels; and
- Aim for IgF-1 level in the middle of normal range for patient based on age and sex unless side effects are significant.

Safety concerns included increase risk of diabetes mellitus and increase risk of tumor growth in recurrence in patients with existing pituitary adenomas.

Though the patient did not fulfill criteria for treatment based on one provocation test, he did have symptoms of growth hormone deficiency, which repeated low for age and sex IgF-1, and at least one pituitary deficiency (hypogonadism) as well as a smaller than normal anterior pituitary gland. Provocation tests can be subject to false negatives and positives; the gold standard insulin tolerance test and the ARG-GHRH test are difficult to conduct in the clinic setting and/or not readily

available as in the case of the ARG testing. His concerns about his family history of early onset coronary artery disease were the deciding factor for treatment. This case illustrates the multiple concerns that need to be addressed in deciding treatment for patients with growth hormone deficiency and that decision needs to be discussed thoroughly before initiation on a case by case basis.

REFERENCES

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