CLINICAL VIGNETTE

Macimorelin: A New Standard Oral Test to Evaluate Adult Growth Hormone Deficiency

Kasra Navabi, MD and Pouyan Famini, MD

Case Presentation

A 29-year-old man with history of growth hormone deficiency (GHD) in childhood presented as a new consult to be evaluated for persistence of GHD and to resume growth hormone deficiency treatment, if indicated.

Physical examination showed a healthy appearing man. Height was 1.829 cm, weight 71.6 kg, blood pressure 119/81, pulse 62, temperature 36.6°C, and O2 saturation 96%. There was no unusual skin pigmentation. He had normal secondary sex characteristics and general exam was normal.

Past medical history included uneventful birth following full-term pregnancy with natural delivery, with normal birth weight and length. Growth during the first 2 years remained consistent at the 25th percentile. From age 3 to age 10, his height moved to the 50th percentile. He was initially evaluated for growth hormone deficiency at age 13.5. His height was 150.5 cm, just above 10%, weight 44.6 kg. Family history is significant for delayed puberty in both parents but otherwise healthy. Father's height was 177.8 cm and mother's height was 162.56 cm. Lab testing at age thirteen showed serum IGF-1 of 150 ng/mL (normal 230-884 for age 13.5), IGF BP3 of 1.8 milligram/liter (normal 2.2-4.2 for age 13.5). Thyroid tests were within normal range. Both serum IGF-1 and IGF BP3 were low for his age and provocation test was performed for confirmation, using the "clonidine/Arginine growth hormone stimulation test". Growth hormone levels were obtained at 30-minute intervals: <0.1 ng/mL, 7.2 ng/mL, 0.2 ng/mL, 1.3 ng/mL, <0.1 ng/mL, on 0 minutes, 30 minutes, 60 minutes, 90 minutes, 120 minutes respectively. Post stimulation growth hormone levels <10 ng/mL are considered abnormal. Pituitary evaluation including MRI were unremarkable. He was diagnosed with growth hormone deficiency and given recombinant human growth hormone 3 mg subcutaneous daily, 6 days of the week. He was treated for 6 years from age of 14 to 18.

Initial consultation included additional baseline morning pituitary hormone testing with the following results: Growth hormone <0.05 ng/mL (normal 0.052-3.0 ng/mL), IGF-1 153 ng/mL (normal 63-375 ng/mL) (Z-score -0.1), testosterone 558 ng/dL (300-1000 80 ng/dL), FSH 2.5 mlU/ml (normal 1.6-9 mIU/mL), LH mlU/ml (normal 2-12 mIU/mL), 5.4, prolactin 15.8 ng/mL (normal 3.8-18.9 ng/mL), ACTH 21 pg/mL (normal 6-59 pg/mL), cortisol 19 mcg/dL (normal 8-25 mcg/dL).

To rule out growth hormone deficiency, a macimorelin stimulation test was performed. The patient received 30 mg (70 mL) of oral reconstituted macimorelin solution over 30 seconds. Serum growth hormone was drawn at intervals of at 30 minutes, 45 minutes, 60 minutes and 90 minutes. The following results were obtained: 16.90 ng/mL, 28.40 ng/mL, 28.10 ng/mL, 13.30 ng/mL and all exceeded the normal threshold of 2.8 ng/mL and ruled out growth hormone deficiency.

Discussion

GH secretion

GH secretion is directly controlled by hypothalamic and peripheral factors acting on GH-secreting cells in the pituitary, known as somatotrophs.[1] Hypothalamic growth hormone-releasing hormone (GHRH) and somatostatin (SRIH) stimulate and inhibit GH secretion, respectively[2] by binding to specific cell-surface receptors on the somatotroph cells.[3] GH secretion is also influenced by metabolic and hormonal signals from other glands, including glucocorticoids, thyroid hormones and sex steroids, which may act directly or via hypothalamic connections. Furthermore, GH regulates its own secretion by a feedback mechanism. Other peripheral mediators, such as IGF-I, free fatty acids, glucose and insulin, can contribute to this feedback mechanism.[4]

GH secretion is also influenced by other peptides and neurotransmitters, including the GH secretagogue (GHS) ghrelin. Ghrelin is a 28 amino acid peptide, produced predominantly by the oxyntic cells in the stomach.[5] It is the natural ligand of the GH secretagogue receptor type 1a (GHS-R1a) and it induces a strong GH-releasing activity upon activating this receptor.[6] The GH-releasing effect of ghrelin is mediated primarily by GHRH-secreting neurons at the hypothalamic level but it also exerts a direct effect on somatotrophs. Ghrelin and GHRH have synergic activities indicating that they have, at least in part, different mechanisms of action.[7]

Growth hormone (GH) deficiency (GHD) is a common finding in adults with acquired hypothalamic-pituitary disorders or persistence of a congenital or acquired somatotroph defect diagnosed in childhood.[8] If GH deficiency occurs in childhood, the deficiency will almost always continue in adulthood unless the diagnosis was "idiopathic GH deficiency" in childhood. Those patients should be retested as adults to confirm

persistence of GH deficiency. The best age for retesting for continuing GHD during the transition period has not been well established.[9]

The most prominent feature of GH deficiency in children is short stature. Individuals who develop GH deficiency in adulthood experience a decrease in lean body mass, bone mineral density (BMD), and quality of life. They also develop increase in fat mass, fracture risk, cardiovascular disease, and mortality.[10] Individuals with childhood-onset GH deficiency that persists into adulthood have more severe clinical manifestations than those who develop it as adults.[11] However, diagnosing this condition is challenging and remains a barrier to initiating GH treatment. Random GH values are non-diagnostic as GH is secreted episodically with low levels between pulses. Other biochemical measurements including IGF-I, IGF-binding protein-3 or GH secretion over a 24-h period have poor diagnostic value with potential overlap between healthy and GH-deficient individuals.[12] Therefore, a GH provocative test is often required to establish the diagnosis with at least one GH stimulation test.[13]

The stimulation tests are performed after an overnight fast. After the pharmacologic agent is administered, serum samples are collected at intervals designed to capture the peak stimulated GH level. The expected time to this peak varies depending on the stimulus. Consensus guidelines recommend that the diagnosis of adult GHD be established in patients with an appropriate clinical history by demonstrating a peak GH concentration of less than 3-5 mcg/L following insulin-induced hypoglycemia (insulin tolerance test, ITT).[8,14] For children, most pediatric endocrinologists defined a "normal" response by a serum GH concentration of >10 mcg/L, but a cutoff of 7.5 mcg/L is often used for modern assays and is used in some countries. This test is well-validated and has long been considered the gold standard by clinical practice guidelines for the diagnosis of AGHD. The test has a sensitivity of 96% and a specificity of 92%.[15] However, this test is labor intensive, has potential risks, and is contraindicated in some patients.

The GH-Releasing Hormone (GHRH) analog (sermorelin) first became commercially available in the United States in 1998. Since then, the combination of arginine (ARG) and GHRH has been validated in several studies and has been suggested as an alternative test by several consensus guidelines when ITT cannot be performed.[16] A major limitation of this test, based on the administration of GHRH, is the risk of missing the diagnosis of AGHD of hypothalamic origin as GHRH directly stimulates somatotroph cells. Thus, it can yield misleadingly normal responses in patients who have a hypothalamic cause of GHD. For many years, the two standard tests have been insulin-induced hypoglycemia or the combination of arginine and GHRH. In 2008, the sole distributor of GHRH in the United States discontinued its production, creating a bigger need for an alternative test. Other stimuli, such as arginine alone, clonidine, L-DOPA, and the combination of arginine and L-DOPA are much weaker and therefore more likely to give false-positive results. All tests of GH secretion are more likely to give false-positive results in obesity. All are performed in the morning after an overnight fast.

More recently, macimorelin, a synthetic agonist of the ghrelin receptor that is active orally has received regulatory approval. The patient must drink the macimorelin solution within 30 seconds and then be observed for the duration of the test. No baseline blood draw is required with macimorelin. After administering the test, venous blood samples are drawn at 30, 45, 60, and 90 minutes. Test results are considered positive for AGHD if the maximally stimulated serum GH level observed after stimulation is <2.8 ng/mL for the 4 blood draws.[17]

There are potential cardiovascular risks. Macimorelin causes an increase of about 11 msec in the corrected QT (QTc) interval. QT prolongation can lead to development of torsade de pointes-type ventricular tachycardia with the risk increasing as the degree of prolongation increases. The concomitant use of macimorelin with drugs that are known to prolong the QT interval should be avoided. Also, the safety and diagnostic performance of macimorelin have not been established for subjects with a body mass index (BMI) >40 kg/m2. The most common adverse reactions to macimorelin are dysgeusia, dizziness, headache, fatigue, nausea, hunger, diarrhea, upper respiratory tract infection, feeling hot, hyperhidrosis, naso-pharynxgitis, and sinus bradycardia.

Macimorelin test requires fewer blood draws than other stimulation tests and eliminates the need for infusion in appropriate patients. With macimorelin, GHD can be tested quickly and efficiently in an outpatient setting.

REFERENCES

1. **Leung KC, Ho KK**. Measurement of growth hormone, insulin-like growth factor I and their binding proteins: the clinical aspects. *Clin Chim Acta*. 2001 Nov;313(1-2):119-23. doi: 10.1016/s0009-8981(01)00662-3. PMID: 11694248.
2. **Hartman ML, Veldhuis JD, Thorner MO**. Normal control of growth hormone secretion. *Horm Res*. 1993;40(1-3):37-47. doi: 10.1159/000183766. PMID: 8300049.
3. **Agrawal V, Garcia JM**. The macimorelin-stimulated growth hormone test for adult growth hormone deficiency diagnosis. *Expert Rev Mol Diagn*. 2014 Jul;14(6):647-54. doi: 10.1586/14737159.2014.915746. Epub 2014 May 16. PMID: 24834478.
4. **Müller EE, Locatelli V, Cocchi D**. Neuroendocrine control of growth hormone secretion. *Physiol Rev*. 1999 Apr;79(2):511-607. doi: 10.1152/physrev.1999.79.2.511. PMID: 10221989.
5. **Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K**. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature*. 1999 Dec 9;402(6762):656-60. doi: 10.1038/45230. PMID: 10604470.

6. **van der Lely AJ, Tschöp M, Heiman ML, Ghigo E**. Biological, physiological, pathophysiological, and pharmacological aspects of ghrelin. *Endocr Rev*. 2004 Jun;25(3):426-57. doi: 10.1210/er.2002-0029. Erratum in: *Endocr Rev*. 2004 Oct;25(5):866. PMID: 15180951.
7. **Hataya Y, Akamizu T, Takaya K, Kanamoto N, Ariyasu H, Saijo M, Moriyama K, Shimatsu A, Kojima M, Kangawa K, Nakao K**. A low dose of ghrelin stimulates growth hormone (GH) release synergistically with GH-releasing hormone in humans. *J Clin Endocrinol Metab*. 2001 Sep;86(9):4552. doi: 10.1210/jcem.86.9.8002. PMID: 11549707.
8. Consensus guidelines for the diagnosis and treatment of adults with growth hormone deficiency: summary statement of the Growth Hormone Research Society Workshop on Adult Growth Hormone Deficiency. *J Clin Endocrinol Metab*. 1998 Feb;83(2):379-81. doi: 10.1210/jcem.83.2.4611. PMID: 9467545.
9. **Grimberg A, DiVall SA, Polychronakos C, Allen DB, Cohen LE, Quintos JB, Rossi WC, Feudtner C, Murad MH; Drug and Therapeutics Committee and Ethics Committee of the Pediatric Endocrine Society**. Guidelines for Growth Hormone and Insulin-Like Growth Factor-I Treatment in Children and Adolescents: Growth Hormone Deficiency, Idiopathic Short Stature, and Primary Insulin-Like Growth Factor-I Deficiency. *Horm Res Paediatr*. 2016;86(6):361-397. doi: 10.1159/000452150. Epub 2016 Nov 25. PMID: 27884013.
10. **Carroll PV, Christ ER, Bengtsson BA, Carlsson L, Christiansen JS, Clemmons D, Hintz R, Ho K, Laron Z, Sizonenko P, Sönksen PH, Tanaka T, Thorne M**. Growth hormone deficiency in adulthood and the effects of growth hormone replacement: a review. Growth Hormone Research Society Scientific Committee. *J Clin Endocrinol Metab*. 1998 Feb;83(2):382-95. doi: 10.1210/jcem.83.2.4594. PMID: 9467546.
11. **Koranyi J, Svensson J, Götherström G, Sunnerhagen KS, Bengtsson B, Johannsson G**. Baseline characteristics and the effects of five years of GH replacement therapy in adults with GH deficiency of childhood or adulthood onset: a comparative, prospective study. *J Clin Endocrinol Metab*. 2001 Oct;86(10):4693-9. doi: 10.1210/jcem.86.10.7896. PMID: 11600527.
12. **Hoffman DM, O'Sullivan AJ, Baxter RC, Ho KK**. Diagnosis of growth-hormone deficiency in adults. *Lancet*. 1994 Apr 30;343(8905):1064-8. doi: 10.1016/s0140-6736(94)90181-3. Erratum in: *Lancet* 1994 Jul 16;344(8916):206. PMID: 7512681.
13. **Ho KK; 2007 GH Deficiency Consensus Workshop Participants**. Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH Research Society in association with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia. *Eur J Endocrinol*. 2007 Dec;157(6):695-700. doi: 10.1530/EJE-07-0631. PMID: 18057375.
14. **American Association of Clinical Endocrinologists**. ACE clinical practice guidelines for growth hormone use in adults and children. *Endocrine Practice*. 1998 May/June; 4(3):165-73.
15. **Biller BM, Samuels MH, Zagar A, Cook DM, Arafah BM, Bonert V, Stavrou S, Kleinberg DL, Chipman JJ, Hartman ML**. Sensitivity and specificity of six tests for the diagnosis of adult GH deficiency. *J Clin Endocrinol Metab*. 2002 May;87(5):2067-79. doi: 10.1210/jcem.87.5.8509. PMID: 11994342.
16. **Aimaretti G, Corneli G, Razzore P, Bellone S, Baffoni C, Arvat E, Camanni F, Ghigo E.** Comparison between insulin-induced hypoglycemia and growth hormone (GH)-releasing hormone + arginine as provocative tests for the diagnosis of GH deficiency in adults. *J Clin Endocrinol Metab*. 1998 May;83(5):1615-8. doi: 10.1210/jcem.83.5.4837. PMID: 9589665.
17. Macrilen [prescribing information]. Plainsboro, NJ: Novo Nordisk Inc; 2021.