

Case Report

Anastrozole Improves Final Adult Height in Severe Hypothyroidism With Rapid Pubertal Progression

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Abbreviations: AI, aromatase inhibitor; GH, growth hormone; GnRHa, gonadotropin-releasing hormone analogue; LT4, levothyroxine; SDS, SD score; TSH, thyrotropin.

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Abstract

Severe prolonged hypothyroidism due to Hashimoto thyroiditis may lead to rapid pubertal progression and compromised adult height after initiation of levothyroxine (LT4) therapy. There are no reports of aromatase inhibitor use to augment height in these patients. We describe a patient with severe hypothyroidism and growth failure who experienced rapid pubertal and bone age maturation on initiation of LT4 therapy. Anastrozole was added after 2 years to delay epiphyseal fusion.

A boy aged 12 years and 1 month presented to the endocrine clinic with short stature and a markedly delayed bone age of 6 years. Brain magnetic resonance imaging showed a 1.5 × 1.0 × 1.2-cm enlarged lobular anterior pituitary. On examination, his height was –3.5 SD score (SDS) and weight was –2.87 SDS. Laboratory studies showed elevated thyrotropin (TSH) 850.6 μIU/mL, low free thyroxine 0.25 ng/dL, and elevated antithyroid antibodies. LT4 was initiated with normalization of TSH after 6 months. After 2 years of treatment he demonstrated catch-up growth with rapid bone age maturation, and his predicted adult height was compromised at 164.6 cm vs a midparental target height of 175.4 cm. Anastrozole 1 mg once daily was initiated. After 1.5 years of anastrozole treatment, the rate of his bone age advancement had slowed and his linear growth remained robust. The patient's near-final height (167 cm) was 2.4 cm taller than his height prediction prior to starting anastrozole.

Anastrozole slowed the rate of bone age advancement in a patient with severe hypothyroidism and rapidly progressive puberty during treatment with LT₄, leading to improvement in near-final height.

Key Words: hypothyroidism, short stature, aromatase inhibitor, bone age

Severe prolonged hypothyroidism due to Hashimoto thyroiditis may lead to early pubertal development, as well as rapid pubertal progression and compromised adult height after the initiation of levothyroxine (LT₄) therapy [1, 2]. Gonadotropin-releasing hormone analogues (GnRHAs) alone or with growth hormone (GH) are unconventional therapies to augment adult height in similar patients [3, 4]. Aromatase inhibitors (AIs) have been used to augment height in patients with idiopathic short stature, GH deficiency, delayed puberty, and in cases of chronic kidney disease and congenital adrenal hyperplasia [5-10].

To our knowledge, there are no reports of AI use to delay bone age advancement and augment growth in patients with treated hypothyroidism. We describe a patient with severe hypothyroidism and growth failure who experienced rapid pubertal and bone age advancement on initiation of LT₄ therapy. Anastrozole was added to delay epiphyseal fusion.



Figure 1. Bone age x-ray at the time of diagnosis, showing a significantly delayed bone age of 6 years at chronological age 12 years 1 month.

Case Presentation

A boy aged 12 years and 1 month presented to the endocrine clinic with short stature, markedly delayed bone age, and concern for a pituitary mass. The patient had a history of short stature since age 7 years and was noted to have decreased growth velocity at his 12-year well-child visit, with height less than the first percentile on the Centers for Disease Control and Prevention growth charts [11]. Bone age radiograph showed a delayed bone age of 6 years at chronological age 12 years (Fig. 1). The radiologist contacted the pediatrician and recommended brain imaging. Magnetic resonance imaging showed a 1.5 × 1.0 × 1.2-cm enlarged lobular anterior pituitary “most likely representative of a pituitary macroadenoma” (Fig. 2). There was no suprasellar extension and mild abutment adjacent to the distal optic nerves. Referral was initially made to the oncology clinic, which subsequently referred the patient to endocrinology and neurosurgery.

The patient was born full term with a birth weight of 6 pounds, 8 ounces. There was maternal heroin use during pregnancy, and he was admitted to the neonatal intensive care unit for 2 weeks after birth. The mother’s height is 165.1 cm and the father’s height is 172.7 cm with a history of mildly delayed puberty. Two older sisters and a younger

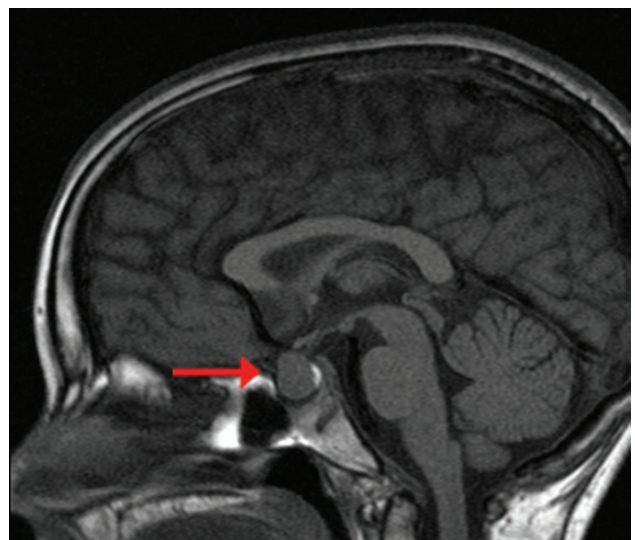


Figure 2. Brain magnetic resonance imaging at the time of diagnosis showing a 1.5 × 1.0 × 1.2-cm enlarged lobular anterior pituitary (arrow), caused by primary hypothyroidism.

half-brother are healthy. There is no known family history of pituitary disease or thyroid disease.

The patient denied any symptoms of headache, vision changes, fatigue, poor sleep, constipation, abdominal pain, dry skin, hair changes, polydipsia, or polyuria. He developed adult-type body odor at age 11 years and denied other pubertal changes.

On physical examination, heart rate was 80 beats per minute, blood pressure 104/66 mm Hg, height 125 cm (-3.5 SD score [SDS]), weight 25.9 kg (-2.87 SDS), and body mass index 16.5 (-0.63 SDS). The patient appeared younger than his stated age. The thyroid gland was palpable but not enlarged. The skin was dry diffusely with lanugo hair present on his back. Hands were cool and doughy in texture. Genitourinary exam showed 8-cc testicles bilaterally with scrotal thinning, normal phallus, and Tanner stage 2 pubic hair. The remainder of the exam was normal.

Laboratory evaluation was obtained at the initial endocrinology visit. Results showed thyrotropin (TSH) 850.6 μ IU/mL, free thyroxine 0.25 ng/dL, elevated antithyroid antibodies, prolactin 45 ng/mL, normal morning cortisol, and low GH markers. LT4 was initiated at 2.4 mcg/kg/d. Follow-up laboratory tests 2 months later showed TSH 19.2 μ IU/mL, and 6 months later TSH 2.6 μ IU/mL. Repeat brain magnetic resonance imaging and laboratory tests after 8 months showed normalization of the pituitary gland size, prolactin, and GH markers.

In the first 2 years of treatment with LT4, the patient demonstrated catch-up growth (9.9 cm/y) and his bone age advanced 7 years (Fig. 3). He had Tanner stage 4 pubic hair and 12- to 15-cc testicles bilaterally. At chronological age 14 years 2 months, his bone age was 13 years with height -2.4 SDS. Predicted adult height, calculated using the methods of Bayley and Pinneau [12], was 164.6 cm (-1.7 SDS). Midparental target height was 175.4 cm (-0.2 SDS). Given concern for compromised growth potential, anastrozole 1 mg once daily was initiated with the goal of delaying epiphyseal fusion. Additional laboratory results and physical exam findings are shown in Table 1.

After 1.5 years of anastrozole treatment, the patient's bone age advanced 6 months with robust linear growth. At chronological age 15 years 9 months, his bone age was 13 years 6 months, with height -1.6 SDS and predicted adult height 178.3 cm ($+0.2$ SDS). The patient had intermittent poor compliance with LT4 and anastrozole treatment. The last bone age obtained was read as 14 years 6 months at chronological age 16 years 5 months. Anastrozole was discontinued after 3 years. Alanine aminotransferase level was monitored during treatment and remained normal. Total testosterone increased as puberty progressed, with the maximum measured level 761 ng/dL while on anastrozole. At the last visit at age 17 years 8 months, growth velocity had decreased to 2.7 cm/y. The patient reached a near-adult height of 167 cm (-1.2 SDS).

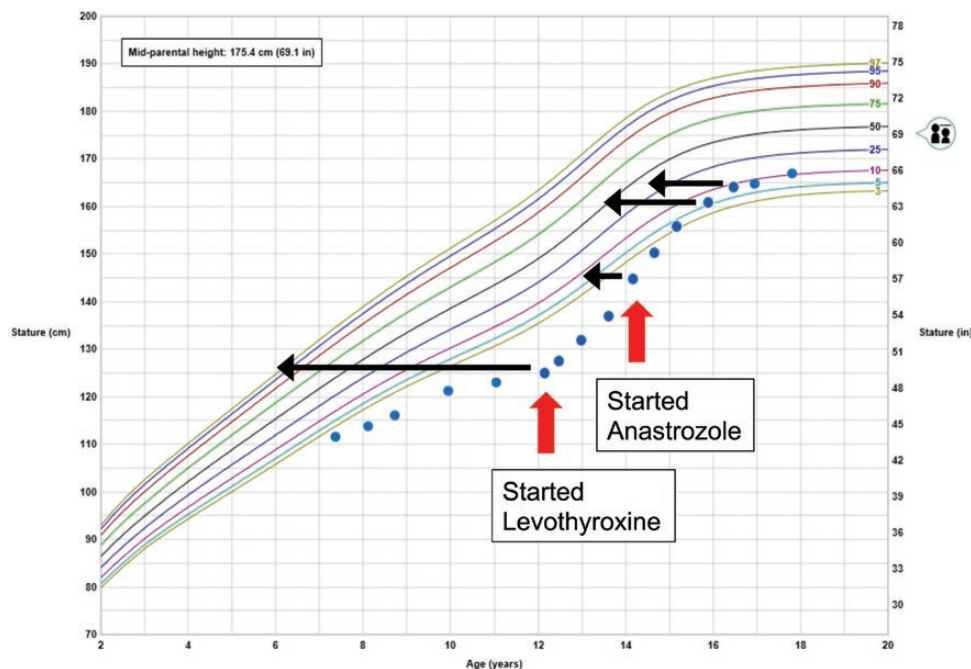


Figure 3. Stature for age growth chart prior to diagnosis, after starting levothyroxine, and after addition of anastrozole. Each circle represents a growth measurement from an office visit at the pediatrician or endocrinologist. Arrows represent bone age x-rays, showing reading of bone age at each time point. Midparental height is marked with a symbol on the right side of the growth chart.

Table 1. Baseline and follow-up laboratory results, growth, and pubertal progression

	Baseline	2-y follow-up	3.5-y follow-up	4.5-y follow-up	5.5-y follow-up
Chronological age	12 y 1 mo	14 y 2 mo	15 y 9 mo	16 y 5 mo	17 y 8 mo
Bone age	6 y	13 y	13 y 6 mo	14 y 6 mo	
Height, cm	125 (−3.5 SDS)	144.8 (−2.4 SDS)	160.8 (−1.6 SDS)	164.2 (−1.4 SDS)	167 (−1.2 SDS)
Growth velocity, cm/y	1.8	9.9	6	6.3	2.7
Predicted adult height, cm	183.8 (+1 SDS)	164.6 (−1.7 SDS)	178.3 cm (SDS + 0.2)	173.2 (−0.5 SDS)	–
Midparental target height, cm	175.4 cm (−0.2 SDS)				
Testicular volume, mL	8	12–15	–	25	–
TSH, μ IU/mL	850.6	2.885	7.872	41.597	4.787
Free T4, ng/dL	0.25	–	1.14	1.04	–
Testosterone, ng/dL	29	985	–	761	–
LH, mIU/mL	–	4.2	–	3.7	–
FSH, μ IU/mL	–	1.9	–	3.2	–
IGF-1, ng/mL	56 (normal, 106–443)				254 (normal, 161–467)
Prolactin, ng/mL	45				5
Treatment	Started LT4 62.5 mcg (2.4 mcg/kg)	Started anastrozole 1 mg daily	LT4 dose increased	Counseling for poor compliance with LT4	Anastrozole discontinued 4 mo prior

Abbreviations: FSH, follicle-stimulating hormone; IGF-1, insulin-like growth factor-1; LH, luteinizing hormone; LT4, levothyroxine; SDS, SD score; T4, thyroxine; TSH, thyrotropin.

Discussion

This case presentation details the outcome of a patient with severe primary hypothyroidism due to Hashimoto thyroiditis who presented with growth delay and developed rapid pubertal progression and bone age advancement after initiation of treatment with LT4. The patient's initial presentation was also significant for pituitary enlargement and initial misdiagnosis of macroadenoma, with normalization of pituitary gland size after treatment with LT4. Pituitary enlargement is frequently present in primary hypothyroidism but is not often evaluated by imaging in the clinical setting [13–15]. The patient had elevated prolactin and low GH markers at presentation, likely a result of severe hypothyroidism because these normalized with LT4 treatment. Owing to rapid bone age advancement, the patient was treated with anastrozole for 3 years. This treatment successfully slowed bone age advancement. The patient initially had bone age progression of 7 years in the first 2 years of treatment with LT4. During treatment with anastrozole for 3 years, the bone age progressed by 1.5 years. His near-final adult height was 167 cm (−1.2 SDS), which was 2.4 cm taller than the predicted adult height prior to initiation of anastrozole and was at the low end of the patient's genetic height potential.

Poor growth is a common presenting sign in pediatric patients with severe hypothyroidism. Thyroid hormone is necessary for linear growth and skeletal maturation, and

patients with hypothyroidism and poor growth typically have delayed bone age at presentation [16]. However, once treatment with LT4 is started, growth and bone age advancement can both occur rapidly. In patients who are in or near puberty, rapid pubertal progression can also lead to a rapid tempo of bone age advancement. Despite treatment, severe hypothyroidism can lead to a permanent decrease in height, which is related to the duration of hypothyroidism prior to treatment [2]. Rapid normalization of thyroid hormone levels has been suggested to cause rapid bone age progression, which both occurred in our patient. No direct correlation between time to euthyroidism and skeletal maturation has been shown, but larger studies and long-term data are needed [17].

Because the bone age is typically delayed in severe hypothyroidism, treatments that can prevent rapid bone age progression could allow for increased time for catch-up growth and height preservation. GnRHa treatment to halt puberty and suppress gonadal steroid production has been used in combination with GH to treat short stature and rapid pubertal progression that can occur after treatment of severe hypothyroidism [3, 4]. These medications are expensive and may not be accessible to all patients. Delaying puberty in older patients also may not be appropriate.

The aromatase enzyme converts androgens to estrogens, and AIs inhibit this action. Estrogen has a major effect on epiphyseal fusion and skeletal maturation

[18]. By decreasing estrogen levels, epiphyseal fusion can be delayed and linear growth prolonged to increase final adult height. AIs have been studied for use in boys with idiopathic short stature, GH deficiency, and delayed puberty [5, 6]. Studies have evaluated the efficacy of AIs used alone or in conjunction with GH [19, 20]. These studies have shown varying results, with some showing improved predicted height and slowing bone age advancement, some showing improved near-final height, and some showing no change in height [5, 6, 19, 20]. Anastrozole and letrozole are third-generation AIs that are used most often to halt growth plate maturation in pediatrics. While letrozole is more potent than anastrozole, efficacy appears to be similar [20, 21].

AIs have also been used to augment height in other conditions causing rapidly advancing bone age and short stature, including congenital adrenal hyperplasia and chronic kidney disease [7-10]. While there have been only case reports of AI use in these diagnoses, results in those cases have shown favorable results with improved height outcomes. In the 3 patients reported with congenital adrenal hyperplasia, there was a significant improvement in final adult height compared to predicted height ranging from 27 to 35 cm after AI treatment for up to 11 years [7-9]. However, 2 patients were also on GnRHa treatment and 1 patient was on GH treatment in the same time frame, which likely also affected height outcomes.

AIs are given as a once-daily oral pill and are relatively cost-effective. Studies of AI use in boys with short stature have identified the following potential side effects: vertebral body deformities, decreased high-density lipoproteins, increased testosterone levels, and increased acne [22-24]. Elevated testosterone levels were more common in patients treated with letrozole compared to anastrozole [21]. Hematocrit levels and transaminases should also be monitored because of potentially increased testosterone levels. There is also concern regarding the effect on spermatogenesis based on mouse studies. Only one study has been conducted in humans to date, showing normal sperm count in adolescent males after treatment with anastrozole [25]. Our patient was treated with anastrozole for 3 years and did not have any evidence of acne or elevated testosterone, transaminases, or hematocrit.

Conclusion

Anastrozole delayed the bone age advancement in a patient with severe hypothyroidism complicated by rapidly progressive puberty during treatment with LT4, leading to improved near-final height. Further studies are needed to

elucidate the effectiveness of anastrozole treatment in these patients.

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Additional Information

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