CASE REPORT

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Short Adult Height After Rapid-tempo Puberty: When is it too Late to Treat?

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What is already known on this topic?

Treatment of growth disorders in puberty involves: gonadotropin-releasing hormone analogues to halt progression of puberty. Growth hormone (GH) to promote linear growth during puberty. Aromatase inhibitors block conversion of androgen, slowing epiphyseal maturation and providing more time for growth. These therapies have been studied in short pubertal individuals having GH deficiency, small for gestational age, idiopathic short stature, SHOX deficiency and central precocious puberty.

What this study adds?

There is a rare unreported phenomenon in which puberty, usually not precocious, advances very rapidly so that testosterone levels rise much more rapidly than is typical. This results in rapid advancement of skeletal age leading to growth being completed early, resulting in short stature. This occurs among brothers and as a consequence may be recognized in a younger brother after occurring in an older brother. This report of five such males using the standard therapies among all but the oldest, and found for the youngest that early therapy preserved or reclaimed adult height (AH) potential. Data also suggest that therapy begun before growth potential is already complete may improve AH.

Abstract

A rarely reported phenomenon of rapid-tempo puberty in which the physical changes of puberty and testosterone levels increase very rapidly has not been reported outside apart from in two reviews. The resulting rapid advancement of skeletal age causes early completion of growth with shorter adult stature than expected. This appears to be genetic given its occurrence in the present report in two families, one with three brothers, one with two. We also describe potential treatments and found for the youngest that early initiation of standard therapy preserved or reclaimed adult height (AH) potential. The foreshortened AH in this situation involves rapidly advancing puberty resulting from high circulating testosterone levels leading to rapid advance in skeletal age. This was recognized earlier among younger brothers and treatment with gonadotropin-releasing analogues, growth hormone (GH) and/or aromatase inhibitor therapy (AIT) was tried. Two brothers in family A and family B were treated. Case 5 started treatment early enough so his AH was within target height (mid-parental height) range. Cases 2, 3, 4 were tried on GH and/or AIT with outcomes suggesting benefit. The prevalence and mechanism of rapid-tempo puberty requires further study. Furthermore, as illustrated by two of the current cases, this phenomenon may have a heightened prevalence, or at least may occur, in children previously diagnosed with constitutional delay of growth, underscoring the need to be cautious in assurance of a normal AH outcomes in this population, based on data from a single assessment.

Keywords: Short adult height, rapid-tempo puberty, male-limited genetic pubertal trait, gonadotropin-releasing hormone analogue, growth hormone, aromatase inhibitor therapy

Introduction

The cases reported here illustrate a phenomenon previously mentioned in only two review articles, which has been called “rapid-tempo puberty” (1,2). This involves an unusual accelerated advance of physical puberty with a rapid maturation of bone age (BA) resulting in foreshortening of adult height (AH) (1,2). Rapid-tempo puberty may be associated with familial patterns, being born small for

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gestational age (SGA), overweight/obesity accelerated early childhood growth, adoption, endocrine disrupters, and delayed treatment of chronic primary hypothyroidism (1). These children have a growth rate along the lower percentiles before puberty and commonly have been evaluated by pediatric endocrinologists who have assured them of normal AH because of BA delay. The physical changes of puberty occur early within the normal age range and progress rapidly with an early growth spurt. However, nothing raises concern until linear growth slows at a height (HT) shorter than expected. By the time this is brought to medical attention, not only is physical development complete, but BA is so advanced that linear growth is also essentially complete and therefore, it is too late for any therapeutic interventions. However, since this may be genetic, younger siblings, especially brothers, may also be at risk and should be evaluated soon after onset of puberty to determine it they may be similarly affected.

A recent review of treatment of short stature during puberty discussed the use of gonadotropin-releasing analogue (GnRHa), growth hormone (GH) and aromatase inhibitor therapy (AIT) among a range of diagnoses, including GH deficiency, SGA, idiopathic short stature (ISS), *SHOX* gene deficiency and central precocious puberty (CPP) (2). An opinion article regarding treatments to delay skeletal maturation to gain AH noted that its effect in short children with normal pubertal timing is equivocal (3). GnRHa therapy is well described for CPP (4) although it has frequently been used during the normal years of puberty (5). A retrospective assessment of growth in ISS patients having early/normal puberty and short adolescents not previously treated with GH found a beneficial effect of combined GH/GnRHa therapy on AH (6,7). A 2016 report of SGA girls treated for two years with GnRHa or GH had similar AHs, if there were adequate growth during GnRHa therapy (7,8). However, a 2023 review which included two of the same authors, found that GH-treated SGA children were still short at the onset of puberty with expected AHs less than -2.5 standard deviation (SD) and have a mean improvement of AH of 6.6 cm (8,9). GnRHa therapy in early pubertal girls with poor predicted AH (PAH) (10) has been reported to result in statistically significant greater AH among a cohort of 16 girls compared with historical controls (11). A publication discussing the use of GH and GnRHa noted that puberty may begin at an appropriate age “but precocious for height age” indicating there may be a positive effect on AH (12). The author found no reports of the use of such therapies, specifically in males with rapid tempo puberty. There is also no reason to assume that the same phenomenon cannot occur in girls who may suffer from referral ascertainment bias. The five cases reported below suggest the genetic nature of rapid-tempo puberty and potential therapeutic approaches to improve AH.

Case Reports

Case 1, presented at 15 years of age, fully mature. He was 167 cm tall and by history had not grown in more than 2.5 years. His father is 178 cm tall and mother 160 cm. Based on his target/mid-parental height (MPH), AH was predicted to be 172.5 cm with a range from 164 and 181 cm.

Case 2, the second of these three brothers, was seen at 12.3 years of age and his BAs, HTs, PAH, weights and treatment are shown in Figure 1. He was then begun on an AIT at 12.6 years of age. It was assumed that the AIT would be effective and he was not fully evaluated until the author first saw him at 15.3 years of age. At this time, by history his voice had changed two years previously at age 13 years. At 15.3 years, his HT was 169.7 cm, considered to be 99% complete. Because knee epiphyses were not yet fused, he continued on anastrozole until he was 16 years old. His near AH at 15.8 years was 170.5 cm.

Case 3, the youngest of the three brothers, was seen elsewhere at 11.6 years with early pubertal development and his HTs, BAs, PAH, and weights are shown in Figure 1. Anastrozole was begun at 12.9 years and GH at 14.1 years when he was first seen by the authors, after potential treatments were discussed. GnRHa was not prescribed, since his BA was considered to be too advanced for this therapy to be potentially helpful. GH was given at 3.2 mg daily (0.37 mg/kg/week), and AIT was changed to letrozole. At 15.3 years, he had grown another 3 cm in 8 months, at which time his family chose to continue the GH and AIT. At 15.8 years, his HT was 170.5 cm, an increase of only 0.8 cm in six months, at which time he was considered to be near AH. GH and AIT were discontinued at this time. AH at 29 years of age, reported separately by the patient and his mother, was 172.5 cm.

Case 4 was healthy as a child, had grown along the 25th percentile for HT and by history had documented delayed BAs. When he was 11.3 years, it was noticed that he had Tanner stage 3 genital development. At 12.3 years, his BA had advanced to 15.2 years (Figure 2) and he was Tanner stage 5. When seen together with his younger brother by the author, further advance in BA and full sexual maturity with testicular volume of 18 cc was noted. Random LH was 2.54 mIU/mL and follicle stimulating hormone (FSH) 1.79 mIU/mL. He was started on GH at an adolescent dosage of 4.5 mg/day (0.5 mg/kg/week) and AIT because of his compromised HT potential. He and his parents understood that his BA age was too advanced for GnRHa therapy to be

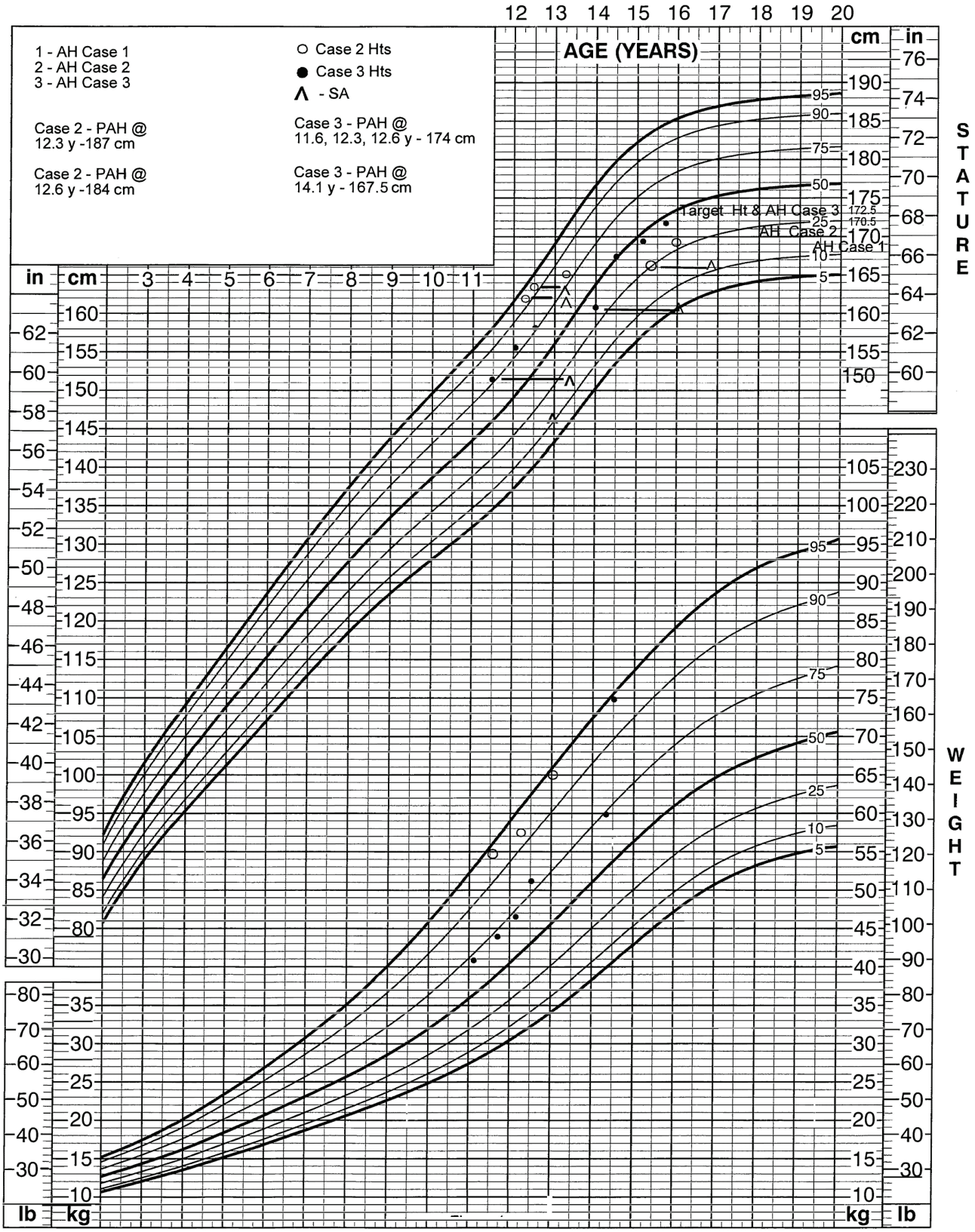

Figure 1. Shows HTs, bone age/SA B weights and PAH for age for Cases 2 and 3. It is apparent that PAHs are not accurate in rapid-tempo puberty. AH of 167 cm is indicated for Case 1. AH for Case 2 and 3 are 170.0 and 172.5 cm respectively

SA: skeletal age, AH: adult height, PAH: predicted adult height

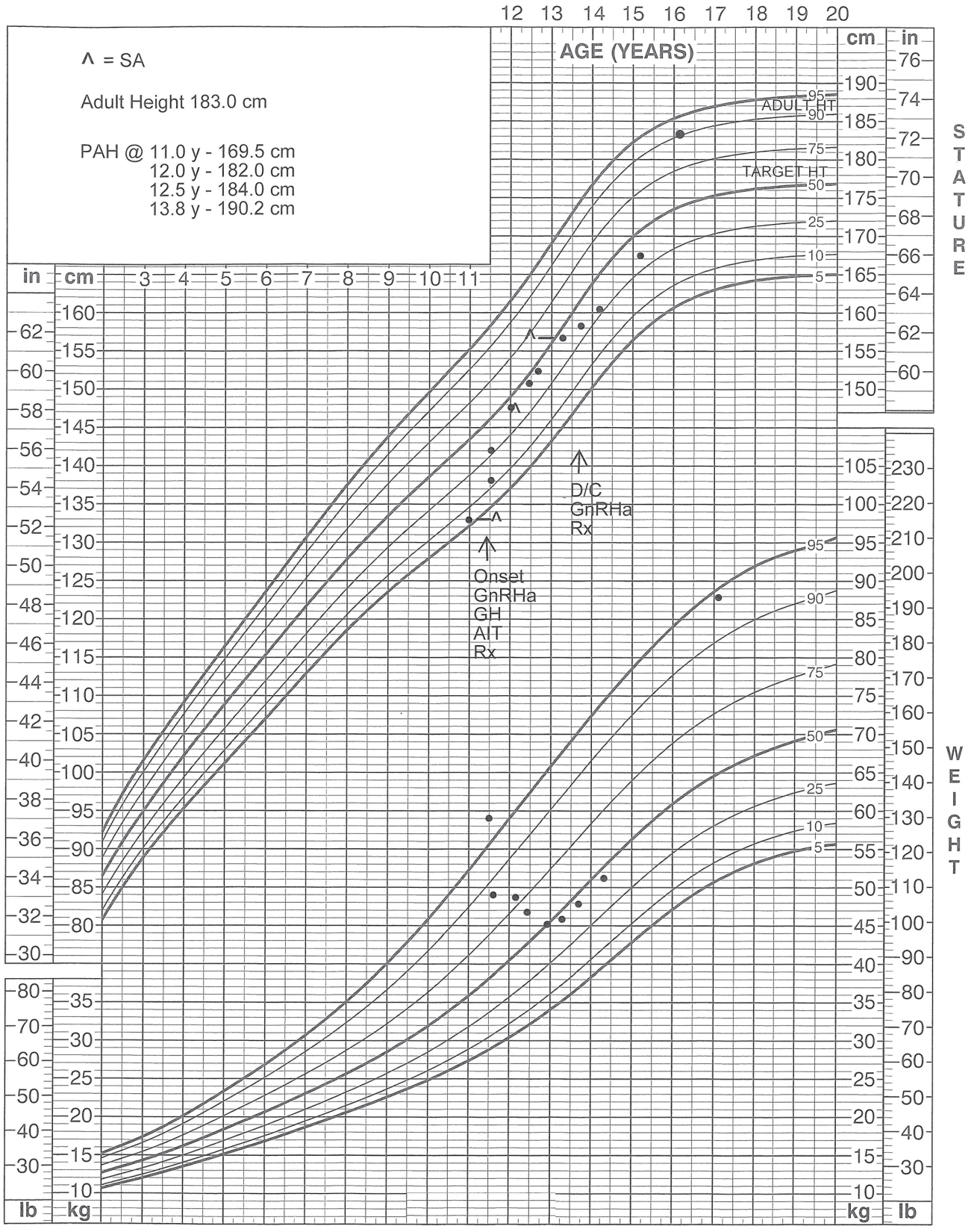

Figure 2. Depicts weight and HT for age, bone age (SA) B of age, treatment, AH, Target/MPH and AH for Case 2. Note that PAH are inaccurate

HT: height, SA: skeletal age, AH: adult height, PAH: predicted adult height, MPH: mid-parental height

helpful. Four months later, at 14.9 years, total testosterone was 1000 ng/dL, IGF1 907 ng/mL and IGFBP3 4.9 mg/L. His HTs and weights were documented four times from age 14.9 to 16.4 years (Figure 2). It is noteworthy that he grew 6.6 cm over the next 1.8 years while receiving GH and AIT. His near AH attained on his 17th birthday was 170 cm, at which time GH and AIT were discontinued. Currently he is 172.5 cm tall at 40 years of age, is married with a healthy child and works as a recruiter for one of the largest companies in the world.

Case 5 had normal birth, neonatal and early developmental histories. From age 3 onward he grew along the 5th percentile for HT; had had BA interpreted as 5 years at 5.8 years of chronological age and again at 8.5 years of age when his BA was read as 8 years. He was seen and evaluated by the author, together with his older brother (Case 4) because he experienced rapid onset of puberty beginning at 11 years and because of his brother's growth history. By history, at 9 years of age, he had developed initial penile growth and body odor, which was followed by recent onset of pubic hair. An accelerated growth rate had been noted within the past year. At 11.0 years, he had another BA which had advanced to 11.5 years with a total testosterone of 158 ng/dL, LH of 0.5 mIU/mL and FSH of 1.4 mIU/mL. His chronological ages, BAs, HTs and weights are shown in Figure 3, together with PAH. When seen at 11.3 years, he had Tanner stage 3 genital development with testicular volumes of 12 cm bilaterally and pubic hair Tanner stage 2. He was begun on three therapies: a) an AIT, using letrozole (2.5 mg/day); b) GnRH analogue therapy (15 mg of leuprolide 4 weeks) to suppress testosterone; and c) GH (2.0 mg/day or 0.22 mg/kg/week).

Four months later, pubic hair had increased to Tanner stage 3. Testosterone had decreased to 15 ng/dL while IGF1 was 341 ng/mL His GH dosage was increased to 2.5 mg daily or 0.24 mg/kg/week). Five months later, his growth in HT continued (Figure 3) while weight decreased further and his testicular volumes had decreased to 10 cc. His BA had advanced by only 6 months to 12 years, consistent with his chronological age, over the 9 months since therapies had begun. IGF1 was repeated and found to be 459 ng/mL. Fifteen months after starting treatment, at 12.4 years, a further decrease was noted in weight to 45.9 kg and in testicular volumes to 8 cc. Testosterone had dropped to <15 ng/dL. Four months later at 12.8 years, his BA was 12.6 years and IGF1 was 481 ng/mL at 13.4 years, his HT and weight had begun to increase. Almost 6 months later at 13.8 years, his age exceeded his BA, which remained at 12.6 years, and there was no increase in testicular volumes. GnRHa therapy was discontinued. Six months later his HT and weight both had further increased, Tanner genital and pubic hair stages were 4 and testicular volumes had slightly increased, providing evidence of resumption of puberty. At age 15 years he weighed 84 kg, and was 167 cm tall, but GH and letrozole were continued as he was still growing at 16.5 years of age. Currently at 26 years of age he is 183 cm tall, healthy and working in cybersecurity tech sales. His AH exceeded his PAH at all times after presentation at 13.0 years, although all data suggest that PAH is often not helpful, since it is based upon the expectation of normal progression of puberty. His AH in relation to his Target/MPH suggests that interruption with appropriate therapies of rapid-tempo puberty can result in AH within the range of Target/MPH, even if well above the mean.

Discussion and Conclusion

It can be assumed that the foreshortened adult HT that occurs with rapid-tempo puberty is the result of elevated circulating testosterone levels resulting in BA advancement, as can be seen with the risk factors that preclude full potential growth in HT that accompany the typical pace of bone maturity. In addition, those caring for prepubertal children with a diagnosis of constitutional delay of growth should be aware of this infrequent entity of rapid-tempo puberty and follow these children closely to catch any accelerated puberty and BA maturation that could have a major adverse effect on ultimate AH. Potential therapy for patients with rapid-tempo puberty recognized before growth is complete, include GnRHa, GH and AIT. Case 1 illustrated that, without intervention, AH is compromised, being at the lower limit (-2 SD) of the range of his Target/MPH. It is not possible to determine if Case 2 benefitted from AIT since his AH is also within the range of his Target/MPH at 169.9 cm, approximately at -1.2 SD. Case 3 appeared to have benefitted from AIT and GH therapy, since his near AH of 170.5 cm was approximately -1.0 SD. Case 4 at 14 years had a PAH of 166 cm and MPH of 175 cm when GH and AIT were begun and reached an AH of 172.5, almost at the mean Target/MPH, strongly suggesting benefit from his therapy (Table 1). Case 5 clearly benefitted from GnRHa therapy until chronological and BA matched, with continuation of GH and AIT, because his AH approached +2 SD.

Case 5, who was started on therapy before his HT potential diminished, even though rapid puberty had begun, suggested that interrupting this process with treatment before high testosterone levels lead to advanced BA and can result in expected AH. The other cases suggest, but do not prove, that both AIT and GH therapy result in greater AH in patients with rapid tempo puberty. Hence, if recognized early, this condition can be successfully treated.

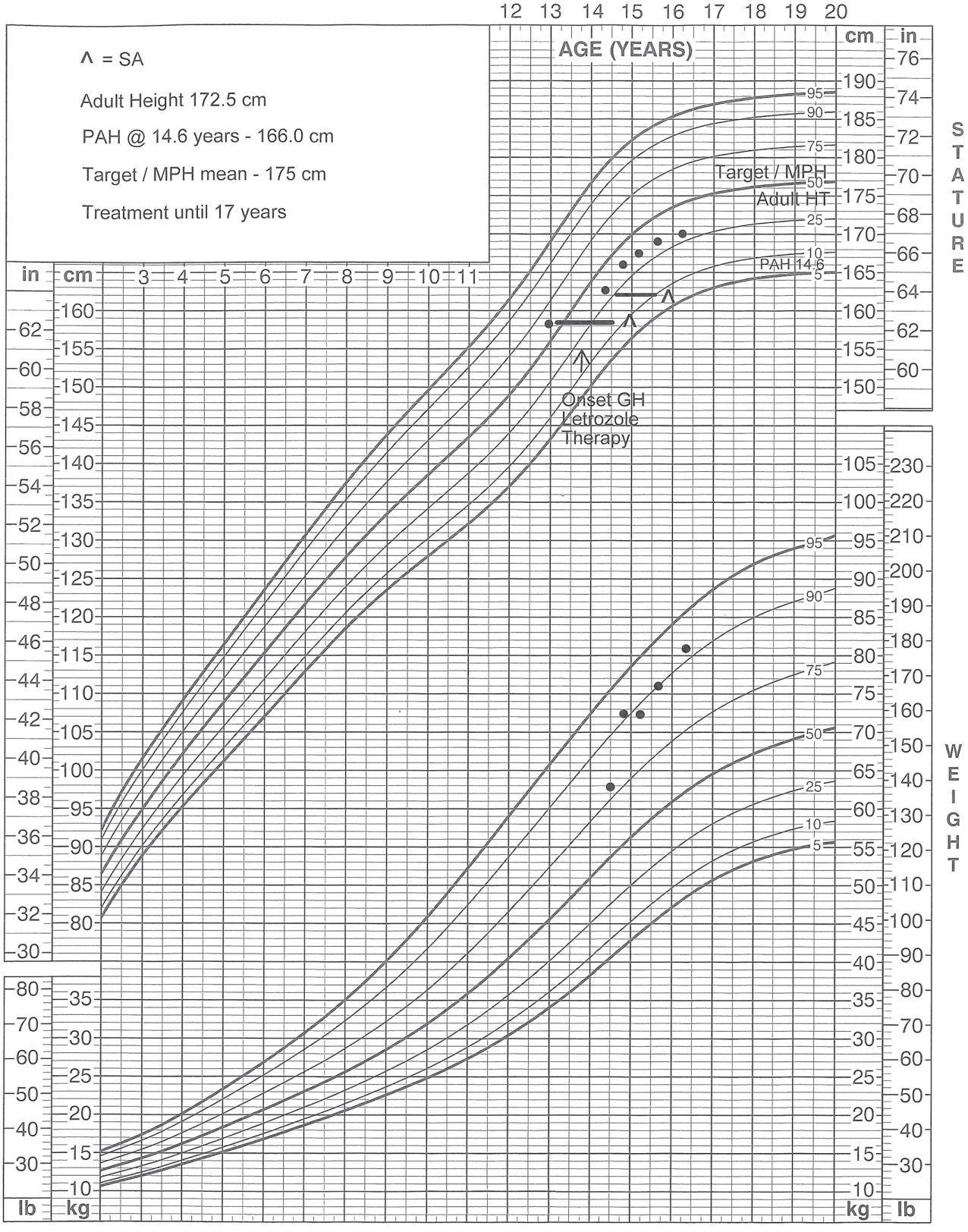

Figure 3. Shows weight and HT for age, bone age or SA for age, treatment, and AH. Note that during GnRHa therapy that SA remained at 12.5 to 13 years during which time HT for age advanced reclaiming lost HT potential. Note also that weight dropped over this interval

HT: height, SA: skeletal age, AH: adult height, GnRHa: gonadotropin-releasing hormone analogue

Table 1. Data from two brothers in family B showing age, skeletal age, height, predicted adult heights, weight and treatment

Family B	Chronologic age (y)	Bone age (y)	Height (cm)	Predicted adult height (cm)	Weight (kg)	Treatment
Case 4	12.3	13.5				None
	13.1	15.2	159.0			
	14.6	16.3	163.4	166.0	63.1	GH and letrozole
	14.9		166.4		71.3	
	15.3		167.5		72.4	
	15.8		168.9		76.6	
	16.4		170.0		79.9	
	40		172.5			None
Case 5	11.0	11.5	133.0	169.5		None
	11.3		138.8		58.8	GH, GnRHa letrozole
	11.6		143.0		48.9	
	12.0	12.0	147.0	182.0	48.00	
	12.4		150.4		45.9	
	12.8	12.5	152.4	184.0	44.9	
	13.4		155.6		46.1	
	13.8	12.5	157.8	190.2	46.1	
	14.3		160.4		50.7	
	15.0		167.0			
	16.5		170.0		84.0	
	26		183.0			None

That the median mid-parental height for sons was 175 cm, with the range from 183.5 to 166.5.
GnRHa: gonadotropin-releasing hormone analogue, GH: growth hormone

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Note: The author, who diagnosed and cared for these patients until late teens and has maintained contact since, wrote this manuscript from that knowledge, medical records and current discussions with the patients and their parents.

Ethics

Informed Consent: Informed consent has been obtained from the patients and they indicated permission to discuss their outcome with their parents.

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