Etiology and Clinical Profile of Patients with Tall Stature: A Single-Center Experience

Alpesh Goyal, Viveka P. Jyotsna, Arun K.C. Singh, Yashdeep Gupta, Rajesh Khadgawat
Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, New Delhi, India

Abstract

Background: There is no published literature on the profile of patients with tall stature (TS) from India. This study aimed to evaluate the etiological and clinical profile of patients with TS referred to our hospital. Materials and Methods: We performed a retrospective review of records of patients referred to us for evaluation of TS (January 2007 to March 2020). Relevant clinical, anthropometric, biochemical, and radiological data at presentation were recorded, and the final diagnosis reviewed. Results: The study included 16 subjects (6 boys, 10 girls) with a mean age at presentation of 13.2 ± 3.6 years. Most subjects were pubertal (n = 10) and belonged to the overweight or obese category (n = 10). The mean height and height standard deviation score (SDS) were 172.3 ± 20.3 cm and 3.6 ± 1.5, respectively, while mean mid-parental height (MPH) and MPH SDS were 168.8 ± 8.8 cm and 1.2 ± 0.9, respectively. The etiological diagnoses were familial TS (n = 9), acrogigantism (n = 3), obesity-related TS (n = 2), constitutional advancement of growth (n = 1), and Marfan syndrome (n = 1). The mean height SDS in subjects with acrogigantism was 6.4 ± 1.2 compared to 3.0 ± 0.6 in those with other etiologies of TS. Only one girl with familial TS and significantly increased predicted adult height (+4.56 SDS) opted for sex steroid therapy. Conclusion: Familial TS is the most common diagnosis among patients referred for evaluation to our hospital. One should consider the possibility of acrogigantism in patients with growth acceleration, extreme TS, and markedly increased gap between height SDS and MPH SDS. Most patients with familial TS require reassurance and sex steroid therapy should be reserved for highly selected cases.

Keywords: Familial tall stature, gigantism, India, pathological tall stature, predicted adult height, sex steroid therapy, tall stature

Introduction

Several factors including nutrition, genetics, socioeconomic factors, and hormones (such as growth hormone (GH), insulin-like growth factor-1 (IGF-1), thyroid hormone, and sex steroids) govern linear growth during childhood and adolescence. Of the various human traits, height is a trait that exhibits normal distribution within each age, gender, and ethnicity. Tall stature is defined as height more than two standard deviations (SD) above the mean for a given age and gender. In a normally distributed dataset, mean ± 2 SD values cover about 95.5% of the population studied. Thus, in a given population, around 2.3 percent of individuals are likely to be tall and equal numbers are likely to be short. However, a referral for assessment of tall stature is sought less often than short stature. The primary reason for this observation is the better acceptability of tallness as a trait in society. Besides, increased height in a child with relatively tall parents is considered to be a reassuring familial trait. A referral to a pediatric endocrinologist is, however, more likely for height >2.5 standard deviation score (SDS) or >3 SDS (extreme tall stature), which include about 0.6% and 0.1% of the population in question. Such cases not only face social adjustment problems, but are also more likely to have an underlying pathological cause for increased growth and, hence, warrant detailed evaluation.

There is no published literature on the profile of patients with tall stature from India. This study aimed to evaluate the etiological and clinical profile of patients with tall stature referred to our hospital.
**Materials and Methods**

**Settings and study design**
We performed a retrospective review of records of patients referred to the pediatric endocrinology clinic of our department for evaluation of tall stature between January 2007 and March 2020. Patients who presented to the hospital for evaluation of another endocrine condition (such as hypogonadism) and had no concern for tall stature were excluded from the analysis. The relevant clinical, anthropometric, biochemical, and radiological data at presentation were recorded, and the final diagnosis reviewed. The protocol for evaluation of patients with tall stature remained almost constant during the study period. Of the 21 cases referred for evaluation of tall stature, a final diagnosis could be reached in 16 who were the subjects for this study. A final diagnosis could not be made in the remaining five cases due to inadequate follow-up, and these were excluded from the analysis. The study was approved by the Institutional Ethics Committee (Ref. No.: IEC-524/05.06.2020, RP-16/2020).

**Anthropometric and pubertal evaluation**
Anthropometric measurements and pubertal assessment were performed using standard methods as detailed in our previous publication.[5] All anthropometric measurements were plotted on KN Agarwal growth charts till December 2019 (n = 15) and on revised Indian Academy of Pediatrics (IAP) growth charts subsequently (January 2020 onwards, n = 1). Girls with breast stage B1 were classified as prepubertal, those with breast stage B2-B4 as pubertal and those with breast stage B5 and onset of menarche as postpubertal. Boys with testicular volume (TV) <4 ml were classified as prepubertal, those with TV between 4 and 15 ml as pubertal and those with TV >15 ml as postpubertal.[9]

Height (and weight) standard deviation scores were calculated using the standard formula. Mid-parental height (MPH) was calculated as an average of father’s height and mother’s height, +6.5 cm for boys and −6.5 cm for girls. MPH SDS was calculated using the formula: MPH SDS = (MPH-Mean final height)/SD for final height.[10] Body mass index (BMI) was calculated as weight (kg)/height squared (m²). Overweight and obesity were defined as BMI corresponding to adult BMI equivalent of 23 and 27 kg/m², respectively, in subjects aged 5–18 years.[8]

**Radiological, biochemical, and other evaluation**
All subjects underwent radiograph of the left hand and wrist for bone age estimation (Greulich and Pyle atlas). Predicted adult height (PAH) or estimated final height (EFH) was calculated using Bayley-Pinneau tables according to the formula: PAH = Current height/fraction of height achieved.[11] PAH SDS was calculated as PAH SDS = PAH-Mean final height/SD for final height.

All subjects were evaluated for GH excess. Serum IGF-1 was used as a screening test for acrogigantism. The diagnosis was confirmed with a GH suppression test performed using a 75 g anhydrous glucose load with blood samples collected at 0, 1, and 2 h. Serum GH and IGF-1 were estimated by a chemiluminescent tracer-based immunometric assay using Diasorin Liaison auto-analyser (Diasorin Inc., Stillwater, MN, USA). Subjects with a biochemical diagnosis of GH excess underwent magnetic resonance imaging (MRI) of the sellar region to look for pituitary adenoma.

Slit-lamp examination and two-dimensional (2D) transthoracic echocardiography were performed in selected cases to look for ectopia lentis and aortic root dilatation. Aortic root diameter was expressed as Z-score, and a score ≥2 indicated aortic root dilatation. Marfan syndrome was diagnosed using revised Ghent criteria.[12]

**Statistical analysis**
The extracted data were manually entered into a pre-coded excel sheet and analyzed using Microsoft Excel software. Data are reported as number (percentage) for qualitative variables and mean ± standard deviation (range) for quantitative variables.

**Results**
A total of 16 subjects (6 boys, 10 girls) with a confirmed etiological diagnosis of tall stature were studied. The clinical and etiological profile of study participants has been shown in Table 1.

**Clinical and anthropometric profile at presentation**
The mean age of study participants was 13.2 ± 3.6 (range, 4-20) years. The mean height and height SDS were 172.3 ± 20.3 (range, 128-213) cm and 3.6 ± 1.5 (2.0-7.2), respectively, while mean MPH and MPH SDS were 168.8 ± 8.8 (range, 155.5-185.0) cm and 1.2 ± 0.9 (range, -0.27 to 2.88), respectively. The mean difference between height SDS and MPH SDS at presentation was 2.4 ± 1.8 (range, 0.07-7.27). The mean BMI was 21.8 ± 5.0 (range, 13.1-31.9) kg/m² (boys: 24.6 ± 4.6 kg/m², girls: 20.1 ± 4.6 kg/m²) and most subjects belonged to overweight or obese category (n = 10). Ten subjects were pubertal, while five were postpubertal and one was prepubertal at the time of initial evaluation.

**Etiological diagnosis of tall stature**
Familial tall stature was diagnosed in nine subjects (56%) who had a height that was increased for the given age and gender (height SDS >2) but appropriate for their genetic potential (height SDS minus MPH SDS <2). An alternative cause for tall stature was excluded in these subjects. Only one subject (case 12, 13-year-old girl) with significantly increased PAH (184 cm, +4.56 SDS) was offered sex steroid therapy, while rest were reassured about the benign nature of their condition (see next section).

Three subjects (cases 3, 14, and 16) were diagnosed to have acrogigantism on the basis of a history of significant growth acceleration, extreme tall stature (height >3 SDS) and biochemical evidence of elevated IGF-1 and unsuppressed
GH. Of these, one subject (case 16) had a history of headache related to the sellar mass lesion, while the other two reported no symptoms of mass effect. All three subjects were detected to have a pituitary macroadenoma on neuroimaging and underwent surgical intervention (see next section).

Constitutional advancement of growth was diagnosed in one subject (case 2) who also had evidence of early puberty, while the diagnosis of obesity-related tall stature was made in two subjects (cases 8 and 9). Subjects in both these groups had tall stature with height minus MPH SDS >2 (see next section). These subjects were reassured and advised weight reduction. Obesity-related tall stature was only diagnosed in subjects who had obesity along with height minus MPH SDS >2. Two subjects (cases 8 and 13) with obesity, but height minus MPH SDS <2 were classified as having familial tall stature (with co-existing obesity).

Marfan syndrome was diagnosed in one subject (case 10) on the basis of presence of tall stature with dysmorphic features, aortic root dilatation, and ectopia lentis (see next section).

The mean height SDS in subjects with acrogigantism was 6.4 ± 1.2 (range, 4.9-7.2) compared to 3.0 ± 0.6 (range, 2.0-4.1) in those with other etiologies of tall stature (n = 13) and 2.9 ± 0.6 (range, 2.0-4.1) in those with familial tall stature (n = 9). Similarly, the mean difference between height SDS and MPH SDS was higher in subjects with acrogigantism (5.3 ± 2.0, range: 3.3-7.2) compared to other etiologies of tall stature (1.7 ± 0.8, range: 0.07-3.18) and familial tall stature (1.4 ± 0.7, range: 0.07-1.92).

**Description of representative case(s) in each etiological category**

**Familial tall stature**
A 13-year-old girl (AK, case 12) presented to us for evaluation of tall stature. She had always been tallest in the class, and her both parents looked relatively tall. Her past medical and family history was unremarkable. Anthropometry revealed height of 176 cm (+4.15 SDS), weight of 61.7 kg (+2.25 SDS), and BMI of 19.91 kg/m² (normal weight). Arm span was 180 cm, and the upper to lower segment ratio was 0.87. Her parents were 184 cm and 170 cm tall, amounting to a MPH of 170.5 cm (+2.27 SDS). Height SDS minus MPH SDS was +1.88. She was pubertal (Tanner stage: B4, P3). On investigation, bone age was 13 years, thyroid function tests were normal, serum GH levels were suppressed on glucose load to a nadir of 0.17 ng/ml, and echocardiography and

**Table 1: Clinical and etiological profile of patients with tall stature evaluated in the study**

| S. No. | ID | Age, sex | Ht (cm) | Ht SDS | MPH SDS | MPH–Ht SDS | Ht–MPH SDS | BMI category | Pubertal Status | Dysmorphism | Comment | Final diagnosis |
|--------|----|----------|---------|--------|---------|------------|------------|--------------|----------------|-------------|---------|----------------|
| 1      | SG | 13, F    | 165     | +2.0   | 158.5   | +0.24      | +1.76      | OW           | Postpub.       | No          | -       | Familial TS    |
| 2      | HA | 18, F    | 149     | +2.59  | 160     | +0.49      | +2.1       | OW           | Pubertal B3, P1| No          | -       | CAG with early puberty |
| 3      | ST | 4, F     | 128     | +7.0   | 155.5   | -0.27      | +7.27      | NA           | Prepub.        | Yes         | GH, IGF-1, PRL incr. Pituitary macroad. |
| 4      | JA | 15, M    | 187     | +3.33  | 185     | +2.88      | +0.45      | NW           | Pubertal       | No          | -       | Familial TS    |
| 5      | SH | 9, F     | 144     | +2.41  | 160     | +0.49      | +1.92      | OW           | Pubertal B2, P1| No          | -       | Familial TS    |
| 6      | AD | 12, M    | 170     | +3.29  | 179     | +1.80      | +1.49      | OW           | Pubertal       | No          | -       | Familial TS    |
| 7      | SA | 14.5, M  | 180     | +2.51  | 174     | +0.91      | +1.60      | OB           | Pubertal       | No          | -       | Familial TS with obesity |
| 8      | DT | 14, M    | 181     | +2.88  | 171     | +0.38      | +2.50      | OB           | Pubertal       | No          | -       | Exogenous obesity with TS |
| 9      | SU | 13.5, F  | 176     | +3.8   | 166     | +1.22      | +2.29      | OB           | Pubertal B4, P4| No          | -       | Exogenous obesity with TS |
| 10     | BA | 20, F    | 178     | +3.54  | 160     | +0.36      | +3.18      | UW           | Postpub.       | Yes         | Ectopia lentis, aortic root dilatation | Marfan syndrome |
| 11     | RB | 15, F    | 170     | +2.68  | 173     | +2.61      | +0.07      | UW           | Postpub. B4, P3| No          | -       | Familial TS    |
| 12     | AK | 13, F    | 176     | +4.15  | 170.5   | +2.27      | +1.88      | NW           | Postpub. B4, P3| No          | -       | Familial TS    |
| 13     | KH | 12, F    | 165     | +2.73  | 165.5   | +1.42      | +1.31      | OB           | Pubertal B3, P2| No          | -       | Familial TS with obesity |
| 14     | VA | 19, F    | 198     | +4.96  | 178     | +1.63      | +3.33      | OB           | Postpub.       | Yes         | GH, IGF-1, PRL incr. Pituitary macroad. | Acrogigantism |
| 15     | PP | 15, F    | 176.9   | +3.15  | 166     | +1.24      | +1.91      | NW           | Postpub.       | No          | -       | Familial TS    |
| 16     | MS | 16.5, M  | 213     | +7.2   | 179.5   | +1.89      | +5.31      | OW           | Postpub.       | Yes         | GH, IGF-1, PRL incr. Pituitary macroad. | Acrogigantism |

BMI: Body mass index, CAG: Constitutional advancement of growth, F: Female, GH: Growth hormone, Ht: Height, IGF-1: Insulin-like growth factor-1, M: Male, Macroad: Macroadenoma, MPH: Midparental height, NW: Normal weight, OB: Obese, OW: Overweight, Postpub: Postpubertal, Prepub: Prepubertal, PRL: Prolactin, SDS: Standard deviation score, TS: Tall stature, UW: Underweight, Wt: Weight
slit-lamp examinations were normal. She was diagnosed to have familial tall stature. PAH was 184.0 cm (+4.56 SDS). The patient and family had a significant concern about her stature. They were explained regarding the effectiveness and short and long-term implications of sex steroid therapy and opted for the same after a detailed discussion. However, she was lost to follow-up subsequently.

A 15-year-old boy (JA, case 4) presented for evaluation of tall stature. His past medical and family history was non-contributory. On anthropometry, height, weight, and BMI were 187 cm (+3.33 SDS), 68 kg (+1.83 SDS) and 19.44 kg/m² (normal weight), respectively. MPH was 185 cm (+2.88 SDS), and height SDS minus MPH SDS was +0.45. Testicular volume was 15 ml bilaterally. Bone age was 16 years, and work-up for alternative causes of tall stature was negative. PAH was 190.4 cm (+3.83 SDS). He was diagnosed to have familial tall stature and reassured about the benign nature of this condition.

**Acrogigantism**

A 4-year-old girl (ST, case 3) presented with a history of rapid increase in height and weight and increased appetite since the age of 1 year. She had an uneventful birth history, and her developmental milestones were normal. Family history was unremarkable. Anthropometry revealed height of 128 cm (+7.0 SDS), and weight of 30 kg (+7.0 SDS). Arm span was 130 cm, and the upper to lower segment ratio was 0.94. She had acral enlargement; there were no café-au-lait macules, areas of bony tenderness, or bony deformities. MPH was 155.5 cm (-0.27 SDS), and the difference between height SDS and MPH SDS was +0.45. Testicular volume was 15 ml. Bone age was 3.5 years. She had an elevated random serum GH level of >80 ng/ml, and MRI of the sellar region revealed a large pituitary macroadenoma with suprasellar and parasellar extension. Serum prolactin was 999 ng/ml (N: 6.0‑29.9 ng/ml), serum thyroxine (T4) and thyroid-stimulating hormone (TSH) were 8.3 μg/dl (N: 5.1‑14.1 μg/dl) and 0.65 μIU/ml (N: 0.27‑4.2 μIU/ml), respectively and serum cortisol was 5.9 μg/dl (N: 6.2‑19.4 μg/dl). She was started on physiological glucocorticoid supplementation and subsequently underwent transnasal transsphenoidal (TNTS) resection of the mass lesion. The postoperative course was complicated by the development of diabetes insipidus and central hypothyroidism. Histopathology confirmed pituitary adenoma with immunopositivity for GH and prolactin and MIB-1 labeling index of 2%. She had persistent biochemical and radiological disease postoperatively. She underwent repeat TNTS procedures at 6 and 12 months and stereotactic radiosurgery at 39 months after the initial intervention. At a latest follow-up visit (aged 8 years), her random serum GH and IGF-1 were 2.8 ng/ml and 329.5 ng/ml (N: 79.8‑244.0 ng/ml), respectively and MRI revealed a suspicious residual lesion of size 6 x 5 mm in the floor of sella. We considered a diagnosis of acrogigantism secondary to X-linked acrogigantism (X-LAG) syndrome, however, genetic testing could not be performed due to resource constraints.

**Obesity-related tall stature**

A 14-year-old boy (DT, case 8) presented to us for evaluation of tall stature and weight gain. Anthropometry revealed height of 181 cm (+2.88 SDS), weight of 50 kg (+3.79 SDS), and BMI of 24.41 kg/m² (obese). MPH was 171 cm (+0.38 SDS), and the difference between height SDS and MPH SDS was increased at +2.50. He was pubertal (bilateral TV of 12 ml). Bone age was 15 years, and work-up for alternative causes was negative. He was diagnosed to have possible exogenous obesity-related tall stature and advised weight reduction.

**Constitutional advancement of growth**

A 9.5-year-old girl (HA, case 2) presented for evaluation for rapid height gain since 2 years. On enquiry, breast development started around the age of 8 years. She had a height of 149 cm (+2.59 SDS), weight of 40 kg (+2.08 SDS), and BMI of 18.02 kg/m² (overweight). MPH was 160 cm (+0.49 SDS), and the difference between height SDS and MPH SDS was increased at +2.10. She was pubertal (Tanner stage: B3, P1). Bone age was 11 years, and work-up for alternative causes was negative. She was diagnosed to have possible constitutional advancement of growth with early puberty and advised weight reduction.

**Marfan syndrome**

A 20-year-old female (BA, case 10) presented to us for evaluation of tall stature. She had been tallest among her peers since childhood. Her family history was non-contributory. The patient attained menarche at 13 years and had regular menstrual cycles. On examination, she had high myopia, arachnodactyly, and positive wrist and thumb sign. Anthropometry revealed height of 178 cm (+3.54 SDS), weight of 47 kg (-0.26 SDS), and BMI of 14.83 kg/m² (underweight). MPH was 160 cm (+0.36 SDS), and the difference between height SDS and MPH SDS was increased at +3.18. Slit lamp examination revealed superotemporal lens subluxation, and a 2D echocardiography confirmed aortic root dilatation. A diagnosis of Marfan syndrome was made according to the Ghent criteria. She was initiated on metoprolol 25 mg, and the need for lifelong cardiovascular surveillance was discussed with her.

**Discussion**

We presented the data on clinical and etiological profile of patients with tall stature referred to our hospital. Most subjects presented for evaluation during the pubertal stage and were either overweight or obese. Familial tall stature was the most common etiological diagnosis, and a pathological cause of tall stature (such as acrogigantism and Marfan syndrome) was evident in a significant proportion of study subjects (n = 4, 25%). All subjects with acrogigantism had a history of growth acceleration and presented with extreme tall stature. The mean height SDS was >2-fold higher in subjects with acrogigantism compared to those with other etiologies of tall stature.

The difference between height SDS and MPH SDS is an important parameter in the clinical approach to a patient with...
tall stature. By definition, all subjects with familial tall stature had height SDS minus MPH SDS <2, implying that their height was increased for the reference population but appropriate for the genetic potential. On the other hand, subjects with other causes of tall stature had height SDS minus MPH SDS of >2, implying that their current height was more than expected for the genetic potential. While the difference was modestly increased (between 2 and 3) in subjects with constitutional advancement of growth and obesity-related tall stature, the increase was more marked (>3) in pathological causes of tall stature such as acrogigantism and Marfan syndrome [Table 1].

Familial tall stature was reported in 9 (56%) subjects and was the most common diagnosis in our cohort. Our observation is in line with published literature on the subject. Acrogigantism was the next common diagnosis and was responsible for 3 (19%) referrals in our cohort. Previous large studies have not reported acrogigantism as a contributing diagnosis in subjects referred for tall stature. [14,15] This unique finding of our study highlights the importance of considering GH excess in subjects with growth acceleration who present with extreme tall stature and a markedly increased gap between height SDS and MPH SDS.

The use of high dose sex steroid therapy to accelerate epiphyseal maturation and reduce final height was once common among girls with familial tall stature. However, this has become less popular in the current day. [16] The factors responsible for the declining use of sex steroid therapy are better social acceptance of tall stature, [17,18] its limited effectiveness (especially when initiated late), [19,20] bothersome short-term side effects, [14] emergence of data on long-term side effects such as subfertility and imminent ovarian insufficiency among treated women, [21-25] and lack of long-term psychosocial benefits. [24-26] Sex steroid therapy should only be offered to patients with significant social concerns who have PAH >2.5 SDS (or 3 SDS). [4] In our cohort, of the nine subjects with familial tall stature (6 girls, 3 boys), only one girl with significant concern about stature and PAH of 184 cm (+4.56 SDS) opted for sex steroid therapy. Other modalities reported in the literature for treatment of familial tall stature include the use of somatostatin analogs and bilateral percutaneous epiphyseodesis of distal femur and proximal tibia. [27-30] However, none of the study subjects received such treatment.

To the best of our knowledge, this is the first study from India to report the etiological and clinical profile of patients with tall stature. The study results were derived from a single center over a period of 13 years, and the protocol for evaluation of patients with tall stature remained almost constant during this period. The limitations of this study are its retrospective design, relatively small sample size, and lack of data on final height of the study participants. Since the study participants were derived from the endocrinology clinic of a large tertiary care hospital, its results may be biased towards a pathological cause of tall stature. While familial tall stature was the most common etiological diagnosis in our study, the proportion of this diagnosis in a population-based survey of tall stature is likely to be higher.

CONCLUSION

This study reports clinical and etiological profile of patients with tall stature referred to a tertiary care center. Familial tall stature was the most common etiological diagnosis. Acrogigantism was the next common diagnosis; this condition should be considered in patients with growth acceleration, extreme tall stature, and a markedly increased gap between height SDS and MPH SDS. Most patients with familial tall stature require reassurance, and sex steroid therapy should be reserved for highly selected cases. Future studies should report the changing trends in referral and treatment patterns of patients with tall stature and final height outcomes.

Author contributions

AG and RK conceived the idea of this work. AG prepared the first draft of the manuscript. All authors read and approved the final version of the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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