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Original Article

Evaluation of Patients with Tall Stature Applying to a Pediatric Endocrinology Clinic

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ABSTRACT

Aim: Tall stature, defined as a height greater than 2 standard deviation score (SDS), affects 2.3% of children. Our study aimed to explore the causes of tall stature in children and assess the long-term outcomes for these cases.

Materials and Methods: This study included 393 children with tall stature who applied to a pediatric endocrinology clinic between 2015-2024. The patients' medical histories, physical examinations, laboratory findings and hormonal profiles were recorded.

Results: Two hundred and forty-seven girls (62.8%) and 146 boys (37.2%) with a mean age of 9.0±2.8 (0.7-16.8) years were included. The majority of the cases presented with obesity and tall stature (25.2%), early onset of puberty signs and tall stature (18.8%), and early onset of puberty signs (12%). Tall stature was not reported as a complaint in 32.7% of the patients. At the initial visit, the height SDS was 2.6±0.5 (2.0-6.2), the mid parenteral height (MPH) SDS was 0.1±0.8 [(-1.9)-3.6] and the predicted adult height (PAH)-MPH was 8.5±7.8 [(-8.5)-39.0] cm. Considering their diagnoses, the majority were familial tall stature (39.9%), obesity + tall stature (32.3%), and central precocious puberty (13.5%). Cranial imaging was performed in 33 cases, and pathology was detected in 10. 95 of the cases had reached their final height. There was a statistically significant difference between the final height SDS and the patients' initial height SDS and MPH SDS values ($p<0.001$). There was no difference between their PAH and final height values ($p=0.481$).

Conclusion: Those individuals with tall stature required fewer hospital admissions than those with short stature. Obesity, precocious puberty, and genetic potential were found to be the most significant triggering factors, so they should not be overlooked.

Keywords: Tall stature, children, final height

Introduction

In children, height >2 standard deviation score (SDS) according to age and gender is defined as tall stature. If the difference between a child's height SDS and mid parenteral height (MPH) SDS is more than 2 SDS, this child can be also defined as a tall child. 2.3% of all children are tall. Tall stature has unfortunately never been a reason for referral as short stature is (1-4).

Height is affected by multiple factors such as nutrition, genetic, hormonal and environmental factors. Growth can be evaluated in four different stages. The first phase is the intrauterine phase and growth in this phase is associated with maternal factors, placental function, maternal nutrition and growth stimulating factors. In the second phase, which includes the first 2-3 years of life, growth is regulated mainly by nutrition. Growth hormone (GH) and

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thyroid hormones play a primary role during childhood in the third phase. In the 4th phase (puberty), a pubertal height spurt is achieved due to the effects of sex steroids along with GH (2).

In the differential diagnosis of tall stature, familial tall stature (FTS) should first be considered (4-8). In tall children without dysmorphic findings, the growth rate must be evaluated first. Healthy obesity, aromatase deficiency or estrogen resistance can be considered in those with normal growth rate and height SDS-MPH SDS>2 SDS. If the difference between MPH SDS and height SDS is less, FTS is particularly considered. If a tall child has an increased height velocity, evaluations should be made for puberty precocious, hyperthyroidism, constitutional tall stature, and GH excess. In tall children with dysmorphic findings, overgrowth syndromes such as Sotos, Weaver, Fragile X, Simpson-Golabi-Behmel (proportionate types) and Marfan, Klinefelter, Beckwith-Wiedemann, Triple X (disproportionate types) must be kept in mind (1-3,9,10).

Tallness is not always benign. There is also the possibility that it may be accompanied by some complications. Cardiovascular system diseases and metabolic disorders, psychiatric problems, vertebral deformities and an increased tendency of breast, prostate and colon cancer are sometimes detected in tall people (4,11,12).

In our study, we aimed to investigate the etiology of children with tall stature who were admitted to the pediatric endocrinology clinic and to evaluate the follow-up of these cases.

Materials and Methods

This study was conducted by accessing the records of 393 tall children (height>2 SDS) who were admitted to our clinic between 2015 and 2024. The patients' complaints at presentation, date of birth, gender, calendar age at the time of admission, weight, height, body mass index (BMI) measurements, bone ages, pubertal stages, final heights and final height SDS, GH suppression test results, pituitary and cranial magnetic resonance imaging (MRI) findings, and the treatments they received were recorded. Data regarding the family history of the patients (birth height, birth weight, MPH, consanguinity, presence of tall individuals in the family, presence of pituitary pathology in the family) were obtained from the hospital database.

Body weight was checked with the same electronic device, and the measurements were taken with the patients wearing just their underwear. The heights of all cases were measured by the same person using a Harpenden Stadiometer. Measurements in the supine position were applied to younger children (under 2 years of age). Height and weight SDS and the height age of the cases were calculated using our country's references (13) and the "CHILD METRICS" program (14). The estimated adult heights of the patients according to their bone ages (predicted adult height=PAH) were calculated via the Bayley-Pinneau method (15). Those cases with a bone age of >14 years in girls and a bone age of >16 years in boys and an annual growth rate of <2 cm were considered to have reached their final heights (16). The heights of the parents were measured and MPH was calculated according to the formula below by using CHILD METRICS:

For girls= [mother's height (cm) + father's height (cm)-13]/2

For boys= [mother's height (cm) + father's height (cm)+13]/2

Tanner staging was used to evaluate pubertal status. Testicular volume was measured with a Prader orchidometer in boys. Testicular volume exceeding 4 mL and breast development in girls at Tanner stage II were considered as entering puberty (17,18). The appearance of secondary sexual characteristics before the age of 8 years on girls and 9 years in boys was considered as precocious puberty (19).

The results of the laboratory parameters in the hospital database [thyroid functions, GH, prolactin, cortisol, insulin like growth factor-1 (IGF-1), insulin-like growth factor binding protein 3 (IGFBP-3), and GH suppression test] were evaluated. Thyroid functions, cortisol and prolactin levels were studied via the chemiluminescent microparticle immunoassay method by Abbott Architect on an I2000 SR device. GH, IGF-1 and IGFBP-3 were studied via the CLIA (chemiluminescent immunoassay) method on a Siemens Immulite 2000 device. IGF-1 and IGFBP-3 SDS values were calculated using CHILD METRICS. Oral glucose tolerance test (OGTT) was performed on those cases with basal IGF-1 and IGFBP-3 >2 SDS, without pre-pubertal/FTS clinics, and/or on those whose height velocity was >1 SDS. GH suppression test was performed by administering 1.75 g/kg glucose orally and then measuring GH levels at 0, 30, 60, 90 and 120 minutes. A GH value of <1 ng/mL was considered as being suppressed (20).

Left wrist radiography of the cases were evaluated and bone age was calculated according to Greulich-Pyle atlas (21). Cases with rapidly progressing puberty, those diagnosed with precocious puberty under the age of 7, and those without precocious puberty but with increased growth rates were evaluated via MRI. The cranial and

pituitary MRI results of the patients were investigated using the data in the records.

Ethical permission was obtained from the Scientific Research Ethics Committee of University of Health Sciences Turkey, İstanbul Ümraniye Training and Research Hospital (approval no.: 79, date: 28.03.2024). A written informed consent form was obtained from the parents of participants.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 27 for Windows (IBM SPSS, Chicago, IL). Descriptive statistics are expressed as mean ± standard deviation for variables with a normal distribution, and as median (minimum-maximum) for variables without a normal distribution. Normal distribution was assessed by the Kolmogorov-Smirnov test. The significance of difference between two pairs was assessed using the Paired Samples t-test. One-way ANOVA was used to compare the means of more than two groups when there was one independent variable. Statistical significance was set at $p<0.05$.

Results

Two hundred and forty-seven girls (62.8%) and 146 boys (37.2%) with an average age of 9.0±2.8 (0.7-16.8) years were included in this study. The majority of the cases presented with obesity with tall stature (25.2%), early onset of puberty signs with tall stature (18.8%), or just early onset of puberty signs (12%). Tall stature was not reported as a complaint in 32.7% of the patients. Birth length was 51.5±2.3 (44.0-58.0) cm and MPH SDS was 0.1±0.8 [(-1.9)-3.6] SDS. There was consanguinity in 19.3% of the participants, and a total of 66.4% stated that there were taller individuals in their family. Additionally, it was learned that 2.3% of the cases had a family history of pituitary pathology. The anthropometric/clinical evaluations of the cases at admission are given in Table I. Considering the diagnoses, the majority were FTS (39.9%), obesity with tall stature (32.3%), and central precocious puberty (CPP) (13.5%). Syndromic tall stature was detected in 1.03% of all cases (4 Marfan, 1 Klinefelter Syndrome) (Table II). There was no significant difference in initial height SDS according to the diagnostic groups (p=0.191).

When the initial laboratory data of the patients were evaluated, no thyroid dysfunction, excess or deficiency of cortisol/prolactin was detected in any of them. OGTT was performed in 68 patients and GH levels were suppressed in all but one (diagnosed with GH secreting adenoma). For the whole study group, IGF-1 SDS was 2.4±2.9 [(-2.4)-21.9] and IGFBP-3 SDS was 1.2±1.1 [(-1.9)-5.6]. When corrected for height age, this data was 0.6±1.5 [(-3.3)-6.4] SDS and 0.6±1.0 [(-1.8)-3.7] SDS, respectively. Cranial imaging was performed in 33 cases, and pathology was detected in 10 of them (2.5% of the entire study group). 8/10 were non-functional microadenomas, 1/10 was GH-secreting microadenoma and 1/10 was hypothalamic hamartoma.

Table I. Anthropometric/clinical evaluations of the cases at admission

Age (year) (min.-max.)	9.0±2.8 (0.7-16.8)
Gender Female (%) Male (%)	 247 (62.8) 146 (37.2)
Height (cm) (min.-max.)	148.1±19.1 (77.5-198.0)
Height SDS (min.-max.)	2.6±0.5 (2.0-6.2)
Weight (kg) (min.-max.)	53.1±21.5 (10-132)
Weight SDS (min.-max.)	2.6±1.0 [(-0.7)-5.5]
BMI (kg/cm^2) (min.-max.)	23.2±5.4 (13.2-45)
BMI SDS (min.-max.)	1.7±1.2 [(-2.9)-4.7]
Pubertal status/Tanner stage Stage 1 Stage 2 Stage 3 Stage 4 Stage 5	 39.4% 26.9% 13.2% 6.2% 14.2%
Bone age (months) (min.-max.)	82.7±62.1 (6.0-204.0)
PAH (cm) (min.-max.)	176.6±11.2 (154.0-207.0)
Height SDS - MPH SDS (min.-max.)	2.5±0.9 [(-1.5)-5.1]
PAH-MPH (cm) (min.-max.)	8.5±7.8 [(-8.5)-39.0]

SDS: Standard deviation score, BMI: Body mass index, PAH: Predicted adult height, MPH: Mid parenteral height, min.: Minimum, max.: Maximum

Table II. Diagnosis of the patients

Diagnosis	**Number (%)**
CPP	53 (13.5)
Obesity	127 (32.3)
FTS	157 (39.9)
Obesity + CPP	25 (6.4)
Marfan syndrome	4 (1)
Obesity + FTS	16 (4.1)
GH secreting adenoma	1 (0.3)
Congenital adrenal hyperplasia	2 (0.5)
Normal variant puberty	7 (1.8)
Klinefelter syndrome	1 (0.3)

CPP: Central precocious puberty, FTS: Familial tall stature, GH: Growth hormone

Table III. Clinical findings of those patients who had reached their final height	
Gender	
Female (%) Male (%)	49 (51.9) 46 (48.4)
Diagnosis	
Obesity +FTS (%) FTS (%) Marfan syndrome (%) CPP (%) Obesity + CPP (%) GH secreting adenoma (%) Klinefelter syndrome (%)	26 (27.4) 60 (63.2) 3 (3.2) 2 (2.1) 2 (2.1) 1 (1) 1 (1)
Final height (cm) (min.-max.)	180.9±9.7 (162.0-210.0)
Final height SDS (min.-max.)	1.8±0.9 [(-0.0)-5.4]
Final height SDS-MPH SDS (min.-max.)	2.4±1.0 [(-1.0)-4.4]
Final height SDS-initial height SDS (min.-max.)	(-0.6)±0.7 [(-2.8)-1.1]
Final height-PAH (cm) (min.-max.)	(-0.2)±6.1 [(-13.4)-23.5]
CPP: Central precocious puberty, FTS: Familial tall stature, GH: Growth hormone, SDS: Standard deviation score, PAH: Predicted adult height, MPH: Mid parenteral height, min.: Minimum, max.: Maximum	

In the follow-up of the patients; gonadotropin-releasing hormone analog treatment was started in 53 patients due to CPP, hydrocortisone treatment was started in two patients due to congenital adrenal hyperplasia, and somatostatin treatment was started in one patient due to GH-secreting adenoma.

It was found that 95 of the cases had reached their final height. The clinical findings of these patients are shown in Table III. There was a statistically significant difference between the final height SDS and the patient's initial height SDS and MPH SDS values ($p<0.001$). We did not find any difference between the PAH and final height values ($p=0.481$). Final heights of both the obesity and FTS groups were found to be higher than the familial target heights. Final height SDS - MPH SDS were 1.51±1.26 in the obesity group and 1.39±0.94 in FTS group. The final height SDS values were lower than initial height SDS levels in these two groups (-0.67±0.74 in the obesity group and -0.64±0.79 in FTS group).

Discussion

In the evaluation of growth, monitoring the height, height velocity and determining whether there are deviations from the normal are very important in the early diagnosis of the presence of any underlying pathological causes (22,23). The evaluation of a tall child begins with creating their medical history. Birth height, weight and head circumference must be investigated. Afterwards, it is crucial to learn about the possible presence of tall individuals in the family, pubertal timing and the auxological parameters of the parents. It is mandatory to have information regarding the child's history of hypo-hyperglycemia, cardiac defects, joint laxity, obesity, nutritional problems, ocular defects and neurodevelopmental disorders. In the physical examination, it is important to evaluate height, weight, head circumference, BMI, sitting height and arm-span (in terms of the differential diagnosis of proportional/disproportionate tall stature) as well as pubertal stage. Also, a detailed examination should be performed in order to detect dysmorphic findings, cardiac murmur, and skeletal deformities. Among our cases, only five patients with syndromic tallness had disproportionately tall stature. For this reason, arm-span and sitting height measurements could not be made in all cases. It is also important to evaluate bone age. In the presence of obesity and early puberty, bone age is advanced; whereas in the presence of FTS, it is normal or retarded. Gonadotropins, GH and IGF-1 levels can be helpful in the differential diagnosis of puberty precocious and GH excess. If disorders of hypothalamic-pituitary axis are considered, detailed hormonal profiles and cranial imaging are useful. Genetic evaluation should be performed in the presence of dysmorphic findings and disproportionate tall stature (1-4,11).

Given that tallness is considered a normal condition, it is not frequently cited as a reason for admission. As a result, patients are often diagnosed late and have an increased likelihood of developing complications (1,2). In 32.3% of our patients, tall stature was not reported as a presenting complaint. The majority of diagnoses were FTS, obesity, and CPP. Consistent with existing literature, the largest group in our study comprised cases with FTS (4,23). FTS was observed in 44% of our patients, and it was noted that 66.4% of all study patients had tall family members. Other studies have reported a frequency of 66-80% for the diagnosis of FTS in children with idiopathic tall stature (24,25).

Obesity and precocious puberty are other frequent causes of tall stature. In our study, 42.8% of the cases had obesity. 19.9% of all cases were followed up with CPP, and two cases were followed up with peripheral precocious puberty. Wang (26) put forward that the prevalence of BMI increased subcutaneous fat tissue and that obesity was higher in girls with early pubertal development than in girls with normal/late pubertal development. Another study reported that increased BMI was associated with early pubertal development and triggered the early onset

of puberty by 0.7 years in girls and 0.6 years in boys (27). In obesity, IGF-1 values are found to be normal/increased due to the effects of high insulin levels. However, the GH response to different stimuli is blunted. Therefore, an increase in height velocity occurs with high IGF-1 levels (28,29). It has also been shown that higher IGF-1 levels in mid-childhood are associated with earlier puberty onset (30). The initial IGF-1 values of our patients were found to be increased, even when it was corrected for height age. However, the GH levels in OGTT were suppressed in all but one individual. The diagnosis of CPP and obesity in a significant portion of our cases may explain the high IGF levels. Except for those case with GH excess, GH suppression in the others indicates that IGF levels may not be sufficient for diagnosis/monitoring. In summary, obese children tend to be 4-5 cm taller than their normal-weight peers. They also tend to have advanced bone age and early pubertal signs (28). When our patients were evaluated, 25 (14%) of 168 obese patients had CPP.

In the differential diagnosis of tall stature, genetic syndromes should be suspected especially if they are accompanied by findings such as dysmorphic findings, disproportionately tall stature and/or pubertal arrest (31,32). The diagnosis rate using molecular genetic methods is 43% in tall cases with syndromic features, but it decreases to 8% in those cases without dysmorphic findings (33). In our study, after clinical and genetic examinations, five patients (1%) were diagnosed with primary growth disorder. 80% of primary growth disorder cases were Marfan Syndrome. Consistent with our findings, in the study conducted by Kärkinen et al. (24), Marfan syndrome was the most common primary growth disorder in extremely tall children with a frequency of 2.3%. Also, it was observed that half of the cases with primary growth disorder had height SDS >3.9 (24). Therefore, as height increased, the probability of primary growth disorder diagnosis increased. The initial height SDS values of our Marfan syndrome cases were 3.18±0.99.

Cranial imaging should be performed especially in the presence of neurological findings and if there is an organic CPP etiology, dysfunction of hypothalamic-pituitary axis should be considered (10). In this study, hypothalamic hamartoma was detected in a male patient who was diagnosed with CPP, and pituitary microadenoma was detected in a female patient who was diagnosed with GH excess.

When the 95 cases who had reached their final height were evaluated, final height SDS was significantly lower than the initial height SDS. However, it was still high compared to the MPH SDS. The fact that the majority of the cases were diagnosed with FTS and obesity may have caused this. Final height data were available for only two CPP cases. Therefore, we could not make an analysis. If treatment for CPP is started earlier and before bone age progresses, it is less likely that there will be a loss in final height (34,35).

PAH values calculated according to the initial bone ages of all cases were compatible with the final height. This highlights the importance of initial bone age assessment.

Study Limitations

When considering the limitations of this study, approximately just a quarter of the cases had reached their final height. There were only two CPP patients who had reached their final height. Therefore, the effect of the treatment on final height could not be evaluated in CPP patients. The annual height velocity of the patients, changes in IGF-1 levels and the relationship of these factors with the final height according to the diagnostic groups also could not be evaluated.

Conclusion

In conclusion, tall stature required fewer hospital admissions than short stature as it was not considered pathological. Obesity, precocious puberty and genetic potential were found to be the most significant triggering factors. Tall stature should not be overlooked by clinicians and possible clinical pathologies should be excluded via detailed evaluations.

Ethics

Ethics Committee Approval: Ethical permission was obtained from the Scientific Research Ethics Committee of University of Health Sciences Turkey, İstanbul Ümraniye Training and Research Hospital (approval no.: 79, date: 28.03.2024).

Informed Consent: A written informed consent form was obtained from the parents of participants.

Authorship Contributions

Surgical and Medical Practices: A.Ö.Ç., I.E., B.Ç., S.E.Ş., M.N.H., Concept A.Ö.Ç., I.E., Design: A.Ö.Ç., I.E., Data Collection and/or Processing: B.Ç., S.E.Ş., M.N.H., Analysis and/or Interpretation: I.E., B.Ç., M.N.H., Literature Search: A.Ö.Ç., I.E., S.E.Ş., Writing: A.Ö.Ç., I.E.

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