http:// ijp.mums.ac.ir
Original Article (Pages: 3355-3361)

Diagnostic Accuracy of Growth Rate in Differentiating Etiologies of Short Stature in Children

Mohammad Reza Alaei[1], *Hedyeh Saneifard[2], Marjan Shakiba[2], Hossein Shabani Mirzaee[3]

[1]Associated Professor of Pediatric Endocrinology and Metabolism, Shahid Beheshti University of Medical Science, Tehran, Iran. [2]Assisstant Professor of Pediatric Endocrinology and Metabolism, Shahid Beheshti University of Medical Science, Tehran, Iran. [3]Assistant Professor of Pediatric Endocrinology and Metabolism, Tehran University of Medical Science, Tehran, Iran.

Abstract

Background

Short stature is a manifestation of a wide variety of conditions that some of which may be amenable to timely treatment and a suboptimal growth rate may be an early marker pointing to the cause of growth retardation. This study was conducted to evaluate the diagnostic utility of growth rate in differential diagnosis of children with short stature.

Materials and Methods

All children between the ages of 2 and 18 years who visited in pediatric endocrinology clinic in a five years period were recruited in a prospective cohort study. Children with standing height <2 standard deviation (SD) below normal for age according to Center Of Disease Control (CDC) charts were enrolled in the study and their growth rates were checked for a period of at least six months. Children who lost their follow-up before six months were excluded. Thyroid function tests were done in all children and growth hormone status, were checked, if deemed necessary.

Results

One hundred forty three patients fulfilled the inclusion criteria. Mean follow up period was 14.4±10.9 months. Etiologies of short stature were: constitutional growth delay (CGD) 46.9%, familial short stature (FSS) 28.7%, hypothyroidism 4.2%, growth hormone deficiency (GHD) 4.2% and miscellaneous causes in 16% of patients. Mean Z- score for children with constitutional growth delay was -2.3±0.69, in familial short stature was -2.3±0.65 and for other condition was -2.7±1.49. There was a meaningful statistical correlation between growth rate and etiology of short stature ($P<0.05$), but there were no correlation between Z-score and etiology of short stature ($P>0.05$).

Conclusion

There was significant difference in growth rate between children with constitutional growth delay and familial short stature in comparing to short stature due to endocrine problem and other etiologies. Assessment of growth rate has some utility in diagnosing the etiology of short stature.

Key Words: Bone age, Constitutional growth delay, Genetic short stature, Growth rate, Short stature.

*Please cite this article as: Alaei MR, Saneifard H, Shakiba M, Shabani Mirzaee H. Diagnostic Accuracy of Growth Rate in Differentiating Etiologies of Short Stature in Children. Int J Pediatr 2016; 4(8): 3355-61.

Corresponding Author:

Hedyeh Saneifard, MD, Assistant Professor of Pediatric Endocrinology and Metabolism, Shahid Beheshti University of Medical Science, Tehran, Iran.

Email: h.saneifard@sbmu.ac.ir

Received date Mar 23, 2016; Accepted date: Jun 22, 2016

1- INTRODUCTION

Short stature is defined as a condition in which an individual has a height that is more than two standard deviation below the average height, for a given age and sex in a reference population (1) and Center for Disease Control and Prevention (CDC) growth charts are the most popular reference for this measurement. Whether a child stature is abnormal purely from a statistical point of view, or whether it is indicative of inadequate growth is a question that need to be defined by additional criteria (2). The importance of growth monitoring in pediatric patients is well recognized. Unduly slow or rapid growth can indicate serious medical conditions, including genetic disorder, chronic disease, infectious disease, and abuse or neglecting and a variety of other problems (3). In general, a growth rate that is abnormally slow, for chronologic and bone age should prompt a thorough examination and possible laboratory evaluation (4).

Key parameters related to growth should be monitored, including length or height according to age, weight, body mass index (BMI) and height velocity compared with the mean of the reference population for boys and girls. In selected children, additional testing will be helpful, such as complete blood count, comprehensive metabolic panel, bone age, Growth hormone (GH), Insulin like growth factor 1(IGF-1) and thyroid stimulating hormone (TSH) / T4 status (5, 6). Recent reports by WHO show that in South-east Asia region a large number of adolescents who constitute about 20% of the population in their countries suffer from malnutrition and anemia, which adversely impact their health and development(7, 8). According to WHO bulletin that was published in 2000, the prevalence of children with height deficit defined as height for age that is more than 2 standard deviation below the reference, has diminished over the last twenty years. In developing countries, about 30.5% of children present such deficit (stunting) (1). The aim of this study was to find out etiologic profile of short stature in children that visited in pediatric endocrinology outpatient clinic and followed for at least six months period. Although we calculate the growth velocity and Z- score of these children to evaluate its importance in following up these children and evaluate the relationship between growth rate and etiologies of short stature.

2- MATERIALS AND METHODS

In a cohort prospective study all children between the ages of 2 and 18 years old who visited in pediatric endocrinology clinic of Loghman Hakim hospital (Tehran- Iran) during a five years period were recruited. All data gathered by an individual pediatric endocrinologist after all the parents signed the informed consent for entering to the study. Children with standing height < 2SD below normal for age were enrolled in the study. Relevant demographic data including age and gender of the child with his/her birth weight and previous medical problems were documented on pre designed forms.

For height measurement, child was undressed and standing erect without footwear against the wall. Arms were placed at the sides of the body, head straight, parallel to the floor and eyes looking straight ahead. Children were then weighed on Secca Scales (Germany). Weight and height of parents were also, measured during initial visit. An anteroposterior radiograph of the left hand and wrist was done for checking the bone age that was estimated according to the Greulich and Pyle atlas of bone age by an individual radiologist that was not informed about medical condition of patients. Thyroid function tests were done in all patients and growth hormone status were checked, if bone age was delayed

>2SD and growth rate was low or the patient had physical signs of GHD. Parameters that were calculated for every child were: Z-score for height at presentation, BMI, Z-score for each parent's height, ΔZ-Score, estimated target height and growth rate.

- Z -score: (Patient's Height - Height for 50% percentile)/SD,
- SD: (Height for 50% - Height for 3%)/1.881,
- Δ Z score: Z- score of patient at the final stage of study – Z score at the initiation of study
- BMI: Weight (kg)/Height^2 (m)
- If, Z- score of patient was >2SD below, his or her parents Z- score it was considered abnormal.
- If Δ Z- score was <0.75, it was considered abnormal.
- Also growth rate less than 4 cm/year was considered an abnormal index.

All enrolled children were followed for a period of at least six months. Their Z-score for height were calculated at the end of follow up and their yearly growth rate determined. Children who lost follow up before six months were excluded from the study. Data were analyses using SPSS for windows (version 16.0) software and Chi-square ($\chi 2$), Fisher's exact test, independent sample t-test and multivariate logistic regression, were applied to analyses the data. P-values <0.05 were considered as the significant levels.

3- RESULTS

One hundred sixty two children between the ages of 2 to 18 years were enrolled that out of these, 143 children completed follow up for at least six months. The mean age was 9.6 ± 3.6 years that 85 (59.9%) were boys and 58 (40.5%) were girls. Height age ranged from 1.5 to 13 years (mean: 7.1±2.9 years old). Bone age estimated for 134 children and ranged from 1.5 to 15.5 years (mean: 7.4±3.8 years old). For a period ranging from 6 to 51 months with a mean follow up period 14.4±10.9 months recruited participant were followed.

Mothers´ height ranged from 140 to 172 centimeters (mean: 154.9±6.5 cm) and fathers´ height ranged from 140 to 189 centimeters (mean=168.5±7.2 cm). The height of 27.5% of fathers and 29.2% of mothers was lower than the 3th percentile on national center of health statistics (NCHS) scale. Using BMI for over 2 years for evaluating nutritional status demonstrated that 16% of our subjects were malnourished that 65.2% of them were boys and 65% over the age of ten.

In survey of hormonal status of children, 6 (4.2%) of short children were hypothyroid (5.9% of boys and 1.7% of girls) and also, 6 (4.2%) of them were growth hormone deficient (4.7% of boys and 3.4% of girls). Mean Z- score results were -2.3±0.9 (boys: -2.3±0.73 and girls: -2.3±1.1). In 74.7% of subjects (75% of boys and 74.3% of girls) Z- score value were between -2 and -3, in 20.9% (19.6% boys and 22.7% girls) Z-score value were between -3 and -4 and 4.4% of them (5.4% boys and 3% girls) Z-score value were <-4. In 27.3% of subjects (27% boys and 27.6% girls) Z- score for height was lower than the range for their parents. In evaluating annual growth rate the mean growth velocity was 6.7±2.9 centimeters that was 7±2.5 for boys and 6.3±3.3 in girls. 19(13.3%) of children (10.6% boys and 17.2% girls) grew at a rate of <4 centimeter per year. Since a ΔZ-score $\leq$ 0.75 was considered subnormal, growth rate was below normal value in 4.9% of subjects (3.5% boys and 6.7% girls). In evaluation of relationship between bone age and growth rate in 65% of children with a normal growth rate, bone age was appropriate for

chronological age while in 35% the bone age lagged behind. On the other hand, in 58.8% of subjects with a slow growth rate, bone age was below the chronological age.
The cause of short stature in children of our study was constitutional growth delay in 46.9%, familial short stature (FSS) 28.7%, hypothyroidism 4.2%, growth hormone deficiency 4.2% and miscellaneous causes in 16% of them respectively (**Table. 1**).

Mean Z- score for children with constitutional growth delay were: -2.3±0.69, in familial short stature was -2.3 ± 0.65 and for other condition was -2.7±1.49.
Results showed that 64 (95.5%) of children with constitutional growth delay and 38 (92.7%) with familial short stature had a normal annual growth rate and only 3 (4.5%) of children with constitutional growth delay and 3(7.3%) with familial short stature had subnormal annual growth rate. However in 6(50%) of subjects with short stature due to endocrine causes and 7(30.4%) with idiopathic short stature the annual growth rate was below normal values (**Table. 2**).

There was significant statistical difference in growth rate between children with constitutional growth delay and familial short stature in comparing to short stature due to endocrine problem and other etiologies (P<0.001), but there was no significant difference between the Z- score of children with short stature caused by different etiologies (P=0.1398).

Table-1: Etiology of short stature in study participants

Etiology	Males, No (%)	Females, No (%)	Total, No (%)
Constitutional short stature	42(61.4)	25(38.5)	67(46.9)
Familial short stature	21(51.2)	20(48.8)	41(28.7)
Hypothyroidism	5(83.3)	1(16.7)	6(4.2)
Growth hormone deficiency	4(66.7)	2(33.3)	6(4.2)
Miscellaneous (cause not identified)	13(56.5)	10(43.5)	23(16)

Table-2: Association of different causes of short stature with growth rate

Etiology	Short growth rate, No (%)	Normal growth rate, No (%)	Total, No (%)
Constitutional short stature	3(4.5)	64(95.5)	67(100)
Familial short stature	3(7.3)	38(92.7)	41(100)
Hormonal	6(50)	6(50)	12(100)
Miscellaneous	7(30.4)	16(69.6)	23(100)

4- DISCUSSION

Growth is an important objective parameter of health in a child. Short stature although not a disease per se, may be a manifestation of several diseases (9, 10). Short stature has been studied extensively worldwide (11, 12). As a definition of short stature, 3% of normal population falls in this category. Any child with an abnormally slow growth rate, height below 3rd percentile, or height considerably below the genetic potential deserves further evaluation (11). Since growth failure has multitude of causes, it is necessary to evaluate a child who is not growing properly (13). The majority of cases of short stature relate to causes considered to be variations from normality (1, 11). This was observed from the literature and in the present study. Thus, highlighting the importance of follow up for such patients and making invasive investigation unnecessary. Sisley et al. reviewed 235 patients with height < 3rd percentile for three years and showed that majority of them are due to variants of normal growth (99%); about them 23% with familial short stature , 41% with constitutional delay of growth and maturation and 36% with idiopathic short stature (14). In another study Shue et al. documented in their studies that normal variants may comprise as much as 65% of short stature of the short children (15).

In the study by Sultan et al. they showed that the most common single etiology of short stature was constitutional growth delay especially in boys (22.1%). In contrast familial short stature affected 27% of girls and only 8.6% of boys. As a group, normal variants of growth, [Constitutional growth delay (CGD) and familial short stature (FSS)] were responsible for 37.9% of short stature (11). In our study, we found that the majority of our patients (75.6%) had familial / constitutional causes and 46.9% of them had constitutional growth delay with mean Z-score: -2.3 ± 0.69 and 28.7% had familial short stature with mean Z- score = -2.3 ± 0.65; thus, reinforcing how it is important for general pediatrician and pediatric endocrinologist to initiate investigations without performing a large part of the follow up for children with short stature.

In this study 75.6% of short stature had non endocrine causes while endocrine causes contribute only 8.4% that out of those 4.2% were due to growth hormone deficiency (GHD). Although, Sultan et al. reported the frequency of GHD, 6.1% in his study (11), and Bhadada et al. in 7.4% of Indian population (13), and 7.9% in Taiwan (15). Other important endocrine etiology was hypothyroidism, diagnosed in 6 (4.2%) of cases in our study. Its incidence in Sultan report (11) was 5.6% and in other studies reported incidences were in close range. We analyzed the relationship between the growth rate (centimeter per year) and bone age and found that most children and adolescents with normal growth rate, had normal bone age (65%) and in patients with inadequate growth rate, 58.8% had abnormal bone age, and we found a meaningful relationship between growth rate and the etiology of short stature ($P<0.001$).

Two studies by Voss et al. (16,17) that followed up children with short stature by comparing them with control cases with normal height, showed that the growth rate cannot distinguish between children with short stature (varying from normality), the children with organic causes for their short stature and control cases. Cianfarani et al. (18) in a study among patients with GHD and idiopathic short stature (ISS) noted that although the growth rate represented a sensitivity over 80%, it showed insufficient specificity, since a growth rate below 25th percentile was observed in the majority of their patients with GHD and also, in almost 60% of the children with ISS. Therefore, the growth rate could not be utilized on its own for identifying the

growth hormone deficiency. The growth rate over any time interval can be assessed via the difference between the Z scores for height with the use of appropriate reference. Van den Broeek et al (19) analyzed the diagnostic validity of growth rate (difference in Z- score) and showed that the diagnostic validity increased when several years of follow up were evaluated and they proposed that for prepubertal children a difference in Z- score≤ -0.75 for a period more than three years could be used as a criterion for future investigations. In the study by Lauzada Strufoldi et al. (1) they utilized the same criterion (Z-score≤ -0.75) for comparison and only two patients presented abnormal Z score (<0.75) . In our study only 4.9% of patients had abnormal Z score difference and 13.3% of our patients had height velocity <4cm/year that is nearly similar to Lauzada Strufoldi results (1). It is very important to know exactly the frequency of various causes of short stature from a given population in order to differentiate normal variants of growth in individual cases of short stature that need early diagnosis and treatment. In addition, growth rate by itself is not capable in guiding the diagnostic investigations.

5. CONCLUSION

Growth hormone deficiency and familial short stature are the leading causes of short stature in children, while GHD is relatively less common. Thus GH axis should only be investigated in selective cases and after adequate monitoring of growth and exclusion of other causes of short stature. Growth rate assessment must form part of the investigation and follow up of short stature. However it has limited diagnostic validity in differentiating etiologies of short stature, as our study revealed that growth rate alone is normal in most different causes of short stature. Although most patients with endocrine problems have subnormal growth rate and it can be used as a clue for more investigations. Its utilization and validity should form part of the analysis of a set of factors: physical examination, radiography for bone age and other complementary tests with the aim of building up an overall view of each patient with short stature.

6- CONFLICT OF INTEREST: None.

7- REFERENCES

1. Louzada Strufaldi MW, Koga da Silva EM, Puccini RF. Follow up of children and adolescents with short stature: the importance of growth rate. Sau Polo Med J 2005; 123(3): 128-33.

2. Ranke MB. Toward a consensus on the definition of idiopathic short stature. Horm Res1996; (4S suppl2): 64-6.

3. Natale V, Rajagopalan A, Worldwide variation in human growth and the World Health Organization growth standards: a systemic review. BMJ open 2014; 4.

4. Allen Db, Cuttler L, Short stature in childhood-challenges and choices. N Engl J Med 2014; 368(13):1220-27.

5. Rogal A, Hayden GF. Etiologies and early diagnosis of short stature and growth failure in children and adolescents. J Ped 2014; 164(5supp1):1-14.

6. Cooke DW, Divall SA, Radvicks S. Normal and aberrant growth. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. Williams textbook of endocrinology. 13th ed. Philadelphia (PA): Saunders Elsevier; 2016.P.935-1053.

7. Patil SS, Patil SR, Durgawale PM, Kakade SV. Study of physical growth standards of adolscents (10-15 years) from Karad, Maharashtra. Int J Coll Res on Int Med and Pub Health 2013; 5(1):10-18.

8. Adolescents Nutrition: A review of the situation in selected South East Asian countries. WHO Regional office of South East Asia. 29 Dec. 2005. Executive Summary.

9. Rabbani MW, Imram Khan W, Bilal Afzal A, Rabbani W. Causes of short stature identified in children presenting at a tertiary

care hospital in Multan Pakistan. Pak J Med Sci 2013; 29(1):53-57.

10. Nicol L, Allen DB, Czernichow P, Zeitler P. Normal growth and growth disorders. In: Kappy M, Allen DB, Geffner M, eds. Pediatric practice endocrinology. New York; Mc Graw-Hill; 2010:23-76.

11. Sultan M, Afzal M, Quresh SM, et al. Etiology of short stature in children. Journal of the College of Physicians and Surgeons Pakistan 2008; 18(8):493-97.

12. Moayeri H, Aghighi Y. A prospective study of etiology of short stature in 426 short children and adolescents. Arch Iranian Med 2004; 7:23-7.

13. Bhadada SK, Agrawal NK, Singh SK, Argwal JK. Etiological profile of short stature. Indian J Pediatr 2003; 70(7):545-47.

14. Sisley S, Trujillo MV, Khoury J, Backeijauw P. Low incidence of pathology detection and high cost of screening in the evaluation of asymptomatic short children. J Pediatr 2013; 163(4):1045-51.

15. Shu SG, Chen YD, Chi CS. Clinical evaluation of short children referred by school screening: an analysis of 655 children. Acta Pediatr Taiwan 2002; 43:340-4.

16. Voss LD, Wilkin TJ, Bailey BJ, Betts PR. The reliability of height and height velocity in assessment of growth. Arch Dis Child1991; 66(7):833-7.

17. Voss LD, Mulligan J, Betts PR, Wilkins TJ. Poor growth in school entrants as an index of organic disease. BMJ 1992:305(6866); 1400-2.

18. Cianfarani S, Tandinelli T, Spadoni GI, Scire G, Boemi S, Boscherini B. Height velocity and IGF-1 assessment in the diagnosis of childhood onset GH deficiency ; do we still need a second GH stimulation test? . Clin endocrinol 2002; 57(2):161-7.

19. Van den Broeck J, Hokken-koelega A, Wit J. Validity of height velocity as a diagnostic criterion for idiopathic growth hormone deficiency and turner syndrome. Horm Res1999; 51(2):68-73.