ORIGINAL ARTICLE

Short stature in Saudi Arabia: etiologic profile in adult endocrine clinic

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Abstract

Background*: To determine causes of short stature (SS) in adult endocrine service at a Saudi Arabian tertiary center.*

Methods: *A retrospective analysis was made of data from 104 subjects who were primarily evaluated for causes of SS in the endocrinology unit of King Khalid University Hospital Riyadh from January 1997 to December 2006.*

Results: *Growth hormone deficiency (GHD) and normal variant short stature (NVSS) were the leading causes of SS contributing 90 subjects (86%; 43% for each), followed by celiac disease in 4 subjects (4%). Other etiologies of short stature included primary hypothyroidism, diabetes mellitus, and Turner's syndrome (2% each).*

Conclusion: *We conclude that GHD and NVSS are the commonest causes of SS in Saudi Arabia. In view of the need to differentiate the two major etiologies, it is suggested that growth hormone stimulatory tests be conducted on all patients with SS associated with delayed bone age. Further prospective study in a larger population is needed to characterize this finding.*

Keywords: *Short stature, etiology, Saudi Arabia*

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Introduction

Short stature (SS) is a common endocrine problem worldwide [1, 2]. Children with SS often experience difficulties ranging from psychological impairment, emotional stress to poor obstetric profile among short females with high maternal mortality in adulthood particularly in developing countries where SS and its complications are increasingly being encountered [3,4]. Knowledge of etiologies of the condition will help in determining differential diagnosis in the local community. With improvement in economic condition and standard of living of Saudi population, more parents have become concerned about growth of their children. This is supported by a recent report showing SS to be the commonest referrals to adolescent endocrine clinic in Saudi Arabia [5]. Yet, until now no studies designed to identify causes of SS in a typical adult tertiary endocrine service in the kingdom. In this study we present data of subjects referred to us for evaluation of SS. We discuss clinical and endocrine aspects and provide an etiological profile of this problem.

Methods

The study is a retrospective analysis of the data of subjects with short stature aged 12 and above who were investigated following referred to or presented at adult endocrine clinic of King Khalid University Hospital Riyadh, Saudi Arabia from January 1997 to December 2006. All hospital admissions were recorded electronically by same medical record staff using codes according to the international classification of diseases (ICD). Data of patients admitted at the hospital with SS during the period were retrieved from the record. One hundred and four subjects with a height more than 3 SD below the mean for their age and sex on Tanner chart were evaluated as previously described [6]. Subjects with incomplete record or clinical suggestion of systemic disease or previously worked up SS under pediatric or adult endocrine care were excluded from the study. For each patient the following information was recorded: chronological age, family history of SS, birth asphyxia, birth weight (if available), and attainment of developmental milestones and long standing diarrhea or abdominal pains as well as usage of medications known to cause short stature. Anthropometric measurements were taken as recommended by Marshall and Tanner [6]. All positive clinical findings detected during general and systemic examination were recorded.

Routine investigations performed included complete blood count, urine examination and biochemical tests including serum concentrations of glucose, urea, creatinine, sodium, potassium, calcium, phosphorus, alkaline phosphatase, total proteins, and albumin. An x-ray of the left wrist was taken in every patient and additional x-rays (elbow, knee and hip-pelvis) were requested in older children to determine approximate bone age according to the atlas of Greulich and Pyle [7]. MRI pituitary was taken in every patient. To assess for

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Turner's syndrome, cytogenetic studies were conducted on every female subject. Serum IgA endomyesial antibody was determined for all patients and upper gastrointestinal endoscopy and biopsy was done for those who had positive antibody. Patients with clinical and radiological evidence of rickets were subjected to urinary acidification test as recommended by Wrong and Davies [8]. Subjects with 24 h urinary volume of more than 50 ml per kg body weight were subjected to dehydration test according to standard protocol.

Basal hormone estimations done included the following: GH, cortisol, triiodotyronine (T3), tetra-iodotyronine (T4), thyroid stimulating hormone (TSH), and gonadotropins. GH stimulation was done with two dynamic tests, insulin tolerance test and clonidine test, as well as one physiologic test in the form of exercise or sleep test. All the GH tests were done in the morning after overnight fast and hormone estimation were performed by specific radioimmunoassay. GH, T3, T4, TSH, and luteinizing hormone estimates were performed by electrochemiluminescence immunoassay (Roche Diagnostics, Indianapolis, IN, USA) with intra-assay and inter-assay coefficient of variation less than 2% and less than 5% respectively.

From history, examination, radiology, and investigations patients were divided into the following major groups:

1. Growth hormone deficiency: defined as SS of <3 SD associated with failure of an increase in serum GH to 10 ug/L or more in response to 2 growth hormone stimulatory tests one of which must be pharmacological in the absence of normal response to any other stimulatory tests [9].
2. Normal variant short stature: defined as SS of <3 SD accompanied by delayed bone age with stimulated peak GH response to >10 ug/L. These patients either had familial short stature or constitutional delay in growth and puberty.
3. Primary hypothyroidism: defined as increased TSH of >10 mU/L in the presence of low FT3 or FT4 or both.
4. Celiac disease: defined as positive serum IgA endomyesial antibody and characteristic histologic finding on endoscopy.
5. Renal tubular acidosis: patients with clinical evidence of rickets with or without nephrogenic diabetes insipidus and with either systemic acidosis and alkaline urine or failure of urine pH to fall below 5.5 after inducing acidosis with ammonium chloride ingestion [10].

The chi-square test was performed to test for association between two categorical factors, and the unpaired t-test was used to assess the relationship between continuous and dichotomous categorical factors. For continuous data that were not normally distributed, the results of t-test were confirmed using the Mann-Whitney test. Results were considered statistically significant at a p value less than 0.05. These analyses were performed using SPSS version 11.0 (Chicago, IL, USA).

Results

Over a period of 10 years, 133 subjects were evaluated for SS at our adult endocrine unit. Twenty-nine subjects were excluded from the study due to incomplete records. The remaining 104 patients comprising 67 males and 37 females were used in this study with a ratio of 1.8: 1. The mean age of subjects at presentation was 15 years ranging from 12 to 21 years. Table I shows the clinical and anthropometric feature of the subjects. The average height at initial visit was less than 140 cm. Table II gives the outline of causes of short stature in our patient population. Growth hormone deficiency (GHD) and normal variant short stature (NVSS) accounted for most (86%) of the causes of SS. Of the 45 subjects with documented GHD, MRI revealed normal pituitary gland in 43 subjects (96%). The only 2 subjects with organic lesions one had craniopharyngioma associated with panhypopituitarism and the other, idiopathic empty sella. Four (8.8%) of those with confirmed GHD were shown to have more than one pituitary hormone deficiency in addition to growth hormone. Other causes included celiac disease 4 (4%), and 2 (2%) each for primary hypothyroidism, diabetes mellitus, and Turner's syndrome. Analysis of the data showed no significant clinical differences between GHD and NVSS as shown in Table 3 while Table 4 compares male with female subjects. Clearly, females were shown to be significantly shorter and having higher body mass index than their male counterparts, $p<0.05$. Other parameters were similar in both sexes.

Table I. Clinical and anthropometric features of 104 subjects with short stature

Parameter	Mean ± SEM	Range
Age (years)	14.8 ± 1.9	12 21
Bone age (years)	11.4 ± 2.7	7 20
Delay (years)	3.9 ± 2.0	1 10
Duration (years)	3.2 ± 1.7	1 5
Weight (kg)	35.8 ± 9.7	20 64
Body mass index (kg/m2)	18.4 ± 4.1	13 32
Father's height (cm)	163.1 ± 7.6	147 180
Mother's height (cm)	155.9 ± 7.2	143 176
Height (cm)	139.0 ± 8.4	117 161
Mid parental height (cm)	160.9 ± 9.4	142 177
Male/female (67/37)	1.8 : 1	-
Positive family history	36 (35%)	-

Table II. Causes of short stature seen at the endocrine clinic

Cause	Number	Percentage
Growth hormone deficiency	45	43
Normal variant short stature	45	43
Celiac disease	4	4
Primary hypothyroidism	2	2
Turner's syndrome	2	2
Diabetes mellitus	2	2
Renal tubular acidosis	1	1
Addison's disease	1	1
Atrial septal defect	1	1
Thalassemia	1	1

Table III. Clinical features of subjects with growth hormone deficiency and normal variant short stature

Parameter	Growth hormone deficiency (45)	Normal variant short stature (45)	p value
Age (years)	14.4 ± 1.6	15.0 ± 2.0	0.1
Bone age (years)	11.5 ± 1.8	11.1 ± 3.2	0.7
Weight (kg)	36.5 ± 8.9	35.6 ± 11.4	0.7
Body mass index (kg/m2)	18.4 ± 3.9	18.6 ± 4.7	0.8
Height (cm)	140.6 ± 8.3	137.9 ± 8.1	0.1
Father's height (cm)	162.6 ± 7.1	162.9 ± 8.5	0.9
Mother's height (cm)	157.3 ± 7.2	155.0 ± 7.7	0.3
Positive family history	13 (29%)	17 (38%)	0.4

Table IV. Clinical and anthropometric features of patients with short stature according to gender

Parameter	Male (67)	Female (37)	p value
Age (years)	14.7 ± 1.6	15.0 ± 2.4	0.4
Bone age (years)	11.2 ± 2.3	12.9 ± 3.9	0.1
Weight (kg)	35.0 ± 9.1	37.1 ± 10.8	0.3
Body mass index (kg/m2)	17.8 ± 3.9	19.5 ± 4.3	0.04
Height (cm)	140.3 ± 8.2	136.7 ± 8.4	0.037
Father's height (cm)	162.9 ± 7.0	163.6 ± 9.0	0.8
Mother's height (cm)	157 ± 6.7	154.9 ± 8.0	0.5
Positive family history	21 (31%)	15 (41%)	0.5
Growth hormone deficiency	27 (40%)	18 (49%)	0.6
Normal variant short stature	32 (48%)	13 (35%)	0.4

Discussion

We have shown that the commonest cause of short stature in adult endocrine clinic to be GHD and NVSS. This is the first review outlining etiologies of SS in Saudi Arabian adolescents as seen in adult endocrine clinic, similar to observation in other parts of the world (11-13). Interestingly it showed higher proportion for both GHD and NVSS in our study population in contrast to consistent reports of lower prevalence in pediatric series. For instance GHD was reported in 8-23% of SS in children below 10 years of age compared to 43% in the current study of predominantly subjects aged 15 years [14, 15]. This might be due to exclusion criteria in which previously diagnosed cases were not included in the study. Furthermore, subjects with clinically obvious underlying medical conditions causing SS could not have been referred to us and were missed for inclusion into the study. In view of the higher percentage of both GHD and NVSS in older children presented in our study, there is a need to subject all patients with SS to growth hormone stimulation tests particularly in those having delayed bone age as the only difference between NVSS and GHD could be normal GH response to the tests in the former. Furthermore, analysis of the data showed no difference in clinical and anthropometric features between the 2 conditions. It is possible that NVSS may be the result of as yet undefined abnormalities.

A closer look at our data revealed idiopathic cause of GHD to be the most commonly encountered variant in subjects with SS in our study population accounting for 96%, similar to others reports [16, 17]. However, intracranial space occupying lesion as a cause of SS leading to GHD was seen in less than 5% in our series in contrast to higher prevalence of 9-11% in earlier reports [15, 18, 19]. This disparity could be due to emergent symptoms of raised intracranial pressure or obvious neurologic deficit which would have led to diagnosis of the etiology of SS at younger age and hence excluded from the study since only undiagnosed cases in subjects older than 12 years of age were included in this review. It is also important to note that there is a limitation to retrospective studies in general. Observations derived from such studies may contain some missing information and thus may serve as a stimulus to further prospective work to clarify findings. The present work must be interpreted in the knowledge of the defects inherent in such studies. Nevertheless, our result is in agreement with other reports [20, 21].

Another interesting aspect of our study was the prominent feature of celiac disease as a cause of SS. We have reported 4% of subjects with gluten-induced enteropathy similar to most reports [22, 23], but differed from Asian series where it was found to be rare cause of SS [11, 15]. However, the result is in keeping with recent observation among native Arabs in whom celiac disease was reported to be common [24]. Other autoimmune diseases seen in our study population include primary hypothyroidism and diabetes mellitus each contributing 2% of the total subjects with SS, consistent with findings in other developing countries [19, 21]. It is important to note that early diagnosis of these conditions often lead to improved quality of life and growth of the subjects. On the other hand, Turner's syndrome was encountered less frequently in our study in which 2% was observed similar to most reports in the literature [13, 23], but in contrast to higher prevalence in Chinese children with SS referred for cytogenetic investigation in whom up to 19% was reported [25]. Another notable difference in this study was the rarity of renal tubular acidosis as a cause of SS in Saudi subjects where we found only 1% of subjects presented with SS having this condition in contrast to 10.4% reported from Indian subcontinent [15]. The reasons for the disparity in prevalence of both Turner's syndrome and renal tubular acidosis could be genetic or environmental factors. Further analysis of gender showed higher proportion of SS among males than

females similar to others observation [14, 15]. Interestingly, we noted no significant differences between the 2 sexes in all clinical and anthropometric aspects except that females tend to be shorter with higher body mass index than their male counterparts. The higher BMI in our female subjects might be due to cultural factor in which males are more likely to engage in physical activities according to school curriculum than females requiring further prospective studies on a larger population to verify this finding.

In conclusion, our data revealed for the first time that GHD and NVSS to be the most commonly encountered cause of short stature in typical adult endocrine clinic in a tertiary centre in Saudi Arabia. In view of the need to differentiate the two etiologies, it is suggested that stimulatory tests be performed on all patients with SS associated with delayed bone age. The study also revealed celiac disease as an important treatable cause of SS in our environment.

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