



Journal of Medical Sciences

ISSN 1682-4474

science
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JMS (ISSN 1682-4474) is an International, peer-reviewed scientific journal that publishes original article in experimental & clinical medicine and related disciplines such as molecular biology, biochemistry, genetics, biophysics, bio-and medical technology. JMS is issued four times per year on paper and in electronic format.

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J. Med. Sci., 16 (3): 56-61
July-September, 2016
DOI: 10.3923/jms.2016.56.61

Idiopathic Short Stature in Children: A Hospital Based Study

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Idiopathic Short Stature (ISS) represents some conditions that are not determinable by current biochemical standards and indicates children who are very short than their mates for indefinite or hereditary reasons. A descriptive observational study of ISS in Saudi children of Taif region. This is a retrospective study carried out from January, 2009 to December, 2014 to survey children with ISS (n = 87) amongst the pediatric population. There were 87 children from 4-17 years of age having ISS and 51.7% were girls. Their evaluation reveal no systemic disease (e.g., growth hormone deficiency or gastrointestinal or thyroid disorder) and no skeletal abnormality. Detailed examination revealed that certain clinical features such as height, weight, arm span, sitting height, subischeal leg length and parental median height were significantly characterized with the short stature patients. The clinic was well accepted by parents and their families. Data reported in this study evaluate and describe a large group of Saudi children with ISS using detailed clinical investigations. Such evaluation helping the decision makers to plan priorities for research and preventive measures.

Key words: Idiopathic short stature, children, endocrinology, growth

INTRODUCTION

Growth is a continuous biologic process depending on several heritable, ecological, nutritional and hormonal effects. Short stature is one of the general reasons for visiting paediatric endocrinologist's clinic. Therefore, in developing countries, short stature represent a serious problem occur in children (Rabbani *et al.*, 2013). Several reports have shown children and adults affected by short stature are at a disadvantage than their peers (Samaras, 2013; Voss, 2006). During childhood, short children are at risk for being hated by their mates by adults (Miller and Zimmerman, 2004). Short adults are also more probably to be hurt in car accidents, because safety tools are devised for average-sized people (Malczyk *et al.*, 2013). Idiopathic Short Stature (ISS) can be defined as short stature without a known pathology reason (Rosenbloom, 2009). Therefore, this definition eliminates the known causes of short stature, which contain numerous forms of GH shortage, familiar genetic conditions such as turner and noonan syndromes, skeletal deformities such as achondroplasia, persistent diseases such as renal failure and inflammatory bowel disease. Also, ISS excludes normal variations in growth pattern, such as inherent delay of growth and development. From a different point of view, ISS may be defined using statistical examination of the distribution of heights at different ages (Bryant *et al.*, 2007; Cohen *et al.*, 2008). Therefore, a person with ISS has a height or length below 3rd centile or less than two standard deviation (-2 SD) for a given age, sex and population group without findings of disease (Bryant *et al.*, 2007; Cohen *et al.*, 2008). Accordingly, it is appraised that about 60-80% of all short stature children suit the definition of ISS (Cohen *et al.*, 2008). As more researchers recognize new causes of short stature, small subsets of the ISS group will be removed from this category. Therefore, it is difficult to identify the cause of short stature in children with ISS by the current diagnostic tools (Miller and Zimmerman, 2004).

The essential and in mean time, most important diagnostic methods for the assessment of short stature continue to be a detailed history examination. This history should include many data such as birth history containing birth weight and height, growth patterns of the patient and family members, facts for pituitary or thyroid dysfunction, nutritional deficiency and signs of chronic illness. Checkup of the growth chart and investigation of parental height are important factor for the history (Miller and Zimmerman, 2004). There is a little quantitative information describing the clinical features in members with short stature group in Kingdom of Saudi Arabia (KSA) (Al-Ruhaily and Malabu, 2009; Al-Jurayyan *et al.*, 2012; El Mouzan *et al.*, 2012).

Thus, this study was conducted to describe and evaluate the detailed clinical investigations of the ISS among children who lived in Taif region, Kingdom of Saudi Arabia.

MATERIALS AND METHODS

The study was conducted and approved in accordance with the research and ethics committee of the participating hospital. Investigators obtained written, informed consent from the participants parents before conducting study related procedures.

This study was conducted at the Prince Mansour Military Hospital, Taif, KSA, from January, 2009 to December, 2014. Eighty seven children from both genders, 4-17 years were recruited in this study. Inclusion criteria for the study were:

- Height below -2 SD to chronological age (Bryant *et al.*, 2007; Cohen *et al.*, 2008)
- Absence of obvious skeletal aberrations and absence of other diseases on physical examination
- Complete physical check, followed by radiological valuation and fitting laboratory screening (complete blood count, erythrocyte sedimentation rate, liver, renal and bone profiles and thyroid function) were assessed and exhibited a normal level
- Normal body ratios (correct proportion among standing height, sitting height, arm span and subischial leg length)
- Normal plasma GH levels
- Normal or low IGF-1 levels for age

Patients with contractures and kyphoscoliosis in whom height could not be measured were excluded. Father and mother height were investigated. Contemporary height was measured without shoes or head gear on an accurate measuring device (Harpenden Stadiometer). Weight of the children was scaled using electronic balance and documented in decimal of kilogram.

Statistical analysis: The results presented as Median±Standard Deviation (SD) for continuous variables. The Microsoft Excel 2010 was used in such analysis.

RESULTS

During the period under study, January, 2009 to December, 2014, a total of eighty seven cases [45 females (51.7%), 42 males (48.3%)] were identified as having ISS; female to male ratio was 1.07:1. All patient samples came from Prince Mansour Military Hospital, Taif governorate, KSA. All children patients had normal karyotypes and were free from causal disorders such as endocrine or skeletal diseases. All children fell below -2 SD deviations. There were 10 (10.3%) children having age less than 6 years, 34 (37.9%) children were between 6-10 years of age, 35 (44.8%) children were between 11-15 years of age, while the rest of 8 (7%) cases were >16 years of age (Fig. 1).

To elucidate the characteristics of growth failure in ISS children patients, the growth pattern in a total 87 patients were analyzed using measurements such as height, arms pan length, sitting height, subscheal leg length and parental median height (Table 1).

Usually scientist used growth charts data from Third National Health and Nutrition Examination Survey and these

Table 1: Anthropometric description of patients separated by gender

Median	Girls (n = 45)	Boys (n = 42)
Chronological age (years)	10.50±6.5	10.10±6.6
Weight (kg)	26.50±16.5	30.20±18.8
Body mass index (BMI) >50th percentile	10 (17.8%)	9 (21.4%)
Height (cm)	116.7±29.6	121.3±28.4
Arm span (cm)	107.2±28.5	113.1±25.2
Sitting height (cm)	64.30±17.5	67.30±18.2
Subscheal leg length (cm)	52.70±13.6	54.40±12.9
Median fathers height	158.0±20.0	161.5±19.5
Median mothers height	155.0±18.0	154.0±15.0
GH level	Normal	Normal
Low level of IGF-I	19 (42%)	14 (33%)

GH: Growth hormone and IGF-I: Insulin-like growth factors-I

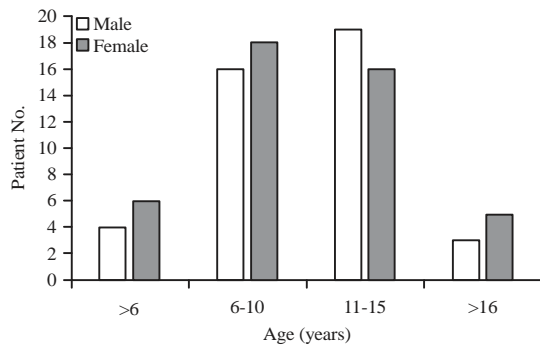


Fig. 1: Age distribution between male and female of the children with idiopathic short stature (n = 87)

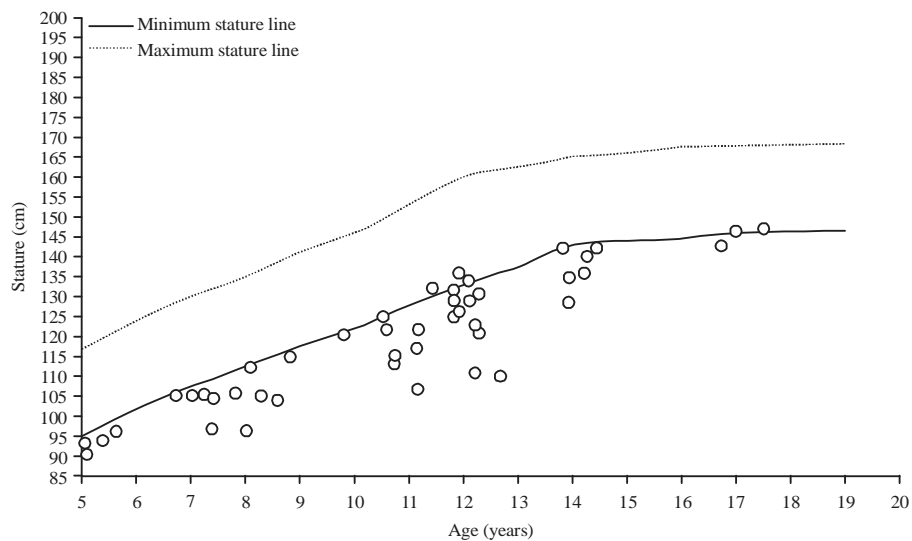


Fig. 2: Distance height chart for each female individuals according to their age with idiopathic short stature [according to the Health Services Council of Saudi Arabia, chart No. 29 (24/6/2007)]

charts are available through the Centers for Disease Control and Prevention (National Center for Health Statistics, 2007). During childhood, linear growth curve is the best and sensitive markers of health. Normal growth is the combined response to several stimulatory and inhibitory signals. A representative distance growth chart for the females and males is shown in Fig. 2 and 3. The medical characteristics of ISS children for females and males show a significant phenotypic variability. Nearly all the 87 patients showed a decrease in linear growth rate with normal or decreased weight (Fig. 2, 3 and Table 1). In general, females appear to be more greatly affected than males (Fig. 2 and 3). Also, the degree of growth deficiency in parental height was decreased than 10 cm compared to the normal adult height (Table 1). It is noteworthy that all patients, in this study, manifested a sustained growth pattern with a normal Growth Hormone (GH) rate (Table 1). By contrast, the Insulin-like Growth Factors-1 (IGF-I) level showed a low concentration in about 42% of female and 33% of male in their blood (Table 1).

DISCUSSION

The evaluation and treatment of short stature is consider to be the second most frequent reason, after diabetes, for the visiting of the clinic of pediatric endocrinologists (Rosenbloom, 2009). It is well known that the evaluation of a child with ISS needs consideration to several attentions like; the medical family history, linear growth data, a full physical analysis and laboratory studies to exclude systemic disease and genetic conditions that associated with short stature (Haymond *et al.*, 2013). This retrospective study was performed to describe a comprehensive clinical scale for ISS. Some studies were done to analyze and describe the short stature in the KSA. Al-Ruhaily and Malabu (2009) were

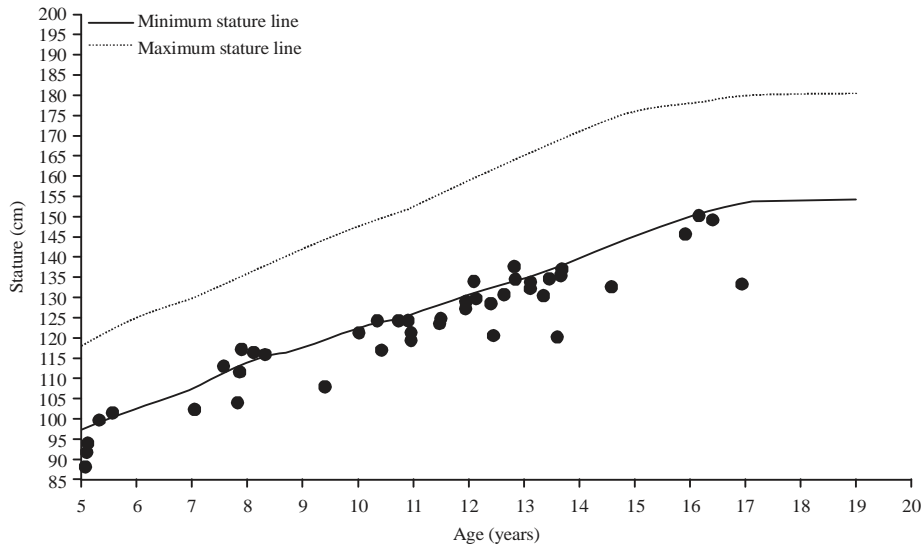


Fig. 3: Distance height chart for each male individuals according to their age with idiopathic short stature [according to the Health Services Council of Saudi Arabia, chart No. 29 (24/6/2007)]

reported the pathologic profile of adult short stature in KSA, while, El Mouzan *et al.* (2012) focused on the regional prevalence of short stature in Saudi school-age children and adolescents. According to their report, there was a meaningfully higher prevalence of short stature in the Southwestern regions (Gizan and Aseer) than in the Northern (Hail, Jof and Northern Borders) or the Central region (Riyadh and Qassim) of KSA (El Mouzan *et al.*, 2012). Another study was conducted to ascertain the aetiological profile of short stature among children patients at King Khalid University Hospital at Riyadh, KSA (Al-Jurayyan *et al.*, 2012). While, this study evaluates the growth and skeletal characteristics of a large group of children with ISS and achieved a thorough analysis of their anthropometric measures (Table 1). Rappold *et al.* (2007), reported that in general short stature is a more frequent reason for boys than for girls. Additionally, the prevalence of short stature from three different regions of the KSA in children from 5-17 years of age were 51% boys (El Mouzan *et al.*, 2012). By contrast, this study found that the ISS was in a greater proportion of tested girls than boys (51.7 vs 48.3%) (Table 1).

It was reported that the -2 SD for height in adult was 164 cm for male and 152 cm for female. Consequently, the median parent's height in this study that ranged between 158-161 cm for male and from 154-155 cm for female height are less than two SD (Table 1). These results are in agreement with the results that stated by Bryant *et al.* (2007), who found that the untreated adult height for males with ISS approximately ranges from 157-170 cm, while, the untreated adult height for females with ISS ranges from about 137-156 cm. Additionally, Gatta *et al.* (2014), stated that there are a decrease about 10-12 cm in the adult height of patients

that having deletion of short stature homeobox gene enhancer and this 10-12 cm estimates the degree of -2 SD of the adult height in the normal population.

As shown in Table 1, there are about 21% females and 18% males patients having BMI values over than 50th percentile. This low frequent is interesting in light of the fact that patients with a working diagnosis of ISS typically have BMI values between low to low normal, possibly because of poor eating behavior (Rappold *et al.*, 2007; Wudy *et al.*, 2005). But, instead of reflecting obesity, the BMI values over than 50th percentile for age and sex in ISS children probably considers segmental disproportion with normal trunk size and short legs (Rappold *et al.*, 2007).

Linear growth chart in healthy children varies meaningfully with age and pubertal status. Changes in growth velocity can be seen when reviewing a child's growth chart. Exact height measurements should be charted at all visits to observe and calculate a height rate (Garganta and Bremer, 2014). Therefore, plotting measurements on a growth chart is essential for recording a child's longitudinal development in size (National Center for Health Statistics, 2007). This is illustrated in this study by the growth charts curves (Fig. 2 and 3). All ISS males and females children in this study prove a decrease in height when comparing to their age equals group's height curve (Fig. 2 and 3).

Linear growth in humans is regulated by many hormonal factors. These factors include GH, IGFs, IGF binding protein-3 (IGFBP-3), thyroid hormone and sex hormones (Katja *et al.*, 2011; Lewitt *et al.*, 2014). Measurement of GH by recurrent serum sampling has been shown to be a useful indicator of GH function. The results showed that all the ISS children patients having normal GH level (Table 1). In comparison to reduced GH rate in patients with endocrine or skeletal diseases, the

normal GH pattern is considered to be characteristic for ISS patients (Dunkel, 2006).

Nevertheless, measurement of GH level is not easily applicable to clinical practice. Therefore, evaluation of serum IGF-1 levels can provide a useful assessment of the GH axis. Because the serum half-life of IGF-1 is longer than that of GH, thus, IGF-1 provides an estimate of GH function (Munoz *et al.*, 2011). In the present study, low IGF-1 levels was found in 42% of female and 33% of male ISS patients (Table 1). As reported by Rosenbloom (2009), this is due to the result of delicate under nutrition or reference to standards appropriate for chronologic age but not bone maturation in constitutional delay in growth and maturation inappropriately labeled as ISS. In ISS children who do not respond to GH treatment, IGF-1 therapy is a theoretical option. Efforts should be made to advance analytical utility by generating better standard information. In the United States, Japan and Europe, IGF-1 is approved for short stature with severe IGF deficiency associated with normal GH secretion (or GH insensitivity) (Cohen *et al.*, 2014).

CONCLUSION

This report establishes the baseline information of ISS in a representative sample of Saudi children at Taif region. More clinical study and development is necessary to ensure and improve the management of these children. The fact that all ISS patients having a normal GH level. Also, it is a well-known that there is an increase in the proportion of consanguineous marriages in the Saudi society. Therefore, in the future, it is urgent to investigate and screen at the molecular level for any possible mutations in some genes related to the stature, e.g., short stature homeobox gene, amongst ISS Saudi children.

ACKNOWLEDGMENTS

The author gratefully thank all the children and their families at the participating study sites who were enrolled in this study.

SIGNIFICANCE STATEMENT

This is a retrospective study describing the clinical investigations of 87 Saudi children patients with idiopathic short stature residing in Taif governorate, KSA.

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