Genetic evaluation of proportionate short stature in Alexandria, Egypt

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ABSTRACT

Introduction: Compared with a genetically relevant population, short stature (ss) is defined as a standing height more than 2 standard deviations below the mean (or below the third percentile) for gender. SS is a common problem for children and adolescents worldwide.

The Aim: This study was conducted to reveal the spectrum of the genetic causes of proportionate ss in Alexandria, Egypt.

Patients and Methods: A total of 120 patients with proportionate SS, (87 girls and 33 males), ages ranging from 6 months to 15 years, selected from the Human Genetic Clinic, Medical Research Institute, Alexandria University, Egypt, were included in this study. All patients were subjected to detailed genetic and family history, clinical genetic examination with particular attention to body proportions and dysmorphic features, anthropometric measurments, radiological examination and chromosomal analysis.

Results: Parental consanguinity was found among 60.4% of the patients. About 37.5% of the cases had positive family history of short stature. It was found that proportionate SS was due to pathologic causes in 87.5% of the cases and to normal growth variants as constitutional growth delay and familial short stature in 12.5% of the cases. Pathologic causes included fetal malformation syndromes (27.2%), genetically determined systemic diseases (23.3%), chromosomal abnormalities (20%), and endocrine disorders (17.6%). About 25% of the studied girls had Turner syndrome.

Accurate diagnosis of SS modifies the management plan for the patient and allows psychological and genetic counseling for the family. Karyotype analysis is recommended for all girls with unexplained SS. A sensitive screening system and an effective referral channel to genetic centers are especially important in the management of SS.

Key Words:

Short stature, genetic etiology, malformation syndromes, chromosomal disorders.

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INTRODUCTION

Adequate lengthening of the skeleton is influenced by genetic, nutritional, environmental and hormonal factors[1] Short stature (SS), optimally defined relative to the genetic endowment of the individual, is recognized by comparing an individual child's height with that of a large population of a similar genetic background and, more particularly, using the mid-parental target height.

Regardless of the genetic background, SS may be a sign of a wide variety of pathologic conditions or inherited disorders. Thus accurate longitudinal growth assessment is a fundamental aspect of health maintenance in children.[1,2]

Short stature (SS) is defined as supine length for children under three years old, or standing height for older children, to be below the third percentile or two standard deviations from the mean height for age of a genetically relevant population[2,3]. The prevalence of SS is about 3% world wide.[4]

Short stature may be proportionate or disproportionate according to the body habitus. Children with disproportionate SS usually have a skeletal dysplasia while those with proportionate SS may have a more generalized disorder.[1,2,5]

The causes of proportionate SS are heterogenous ranging from genetic pathological causes to normal growth variants such as familial SS and constitutional delay in growth and maturation. Pathological causes include systemic disease, endocrine disorder, psychological dwarfism, genetic syndrome or a chromosomal or a teratogenic disorder.[4,5]

Short stature should not be overlooked because the underlying medical conditions must be detected and treated before fusion of the epiphysis.[2,5]

Accurate diagnosis of SS modifies the management plan for the patient and indicates psychological as well as genetic counseling for the family[1,3]. This study was conducted to reveal the spectrum of the genetic causes of proportionate SS in Alexandria, Egypt.

PATIENTS AND METHODS

This study included 120 patients with proportionate short stature (87 females and 33 males). Ages ranged from 6 months to 15 years. They were selected from the Human Genetic Clinic, Medical Research Institute, Alexandria University, Egypt.

All patients were subjected to detailed genetic and family history; including the child's weight and length at birth, the final heights, weights and pubertal timing in the parents and siblings; with pedigree construction. Clinical genetic examination with particular attention to body proportions, dysmorphic features, midline defects, and systems review for chronic illness. Anthropometric measurements were carried out according to Tanner et al.[6] The standing height in children or recumbent length in infants, was determined and plotted on Egyptian control chart[7]. In cases, who can't completely stand or recline (e.g. those with spina bifida and/or contractures) arm span provides a reliable alternative for longitudinal assessment of long bone growth. Head circumference and weight measurement are essential. Arm span to height ratio (around 1.0 at all ages), together with sitting height to lower body

segment (in newborn around 1.7, which gradually drops to approximately 1 by 10-12 years and remains just below 1.0 in adulthood) are important to confirm the diagnose of proportionate SS.[2]

Radiological examination (including skeletal survey and bone age examination), and chromosomal analysis using G-banding technique were done[8]. Other investigations were performed when indicated to confirm diagnosis e.g. hormonal assay, urine screening, Hb electrophoresis, ultrasonography, ECHO and CT scan.

RESULTS

This study included 120 patients (87 females and 33 males) with proportionate short stature. Ages ranged from 6 months to 15 years. The female to male ratio was 2.6:1.

The studied cases were classified according to the genetic etiology into; pathological SS (105 cases) and normal growth variants (15 cases)(Table 1).

For the group with pathological causes of proportionate SS, 33 cases (27.5%) had syndromal disorders. [19 autosomal dominant, 12 autosomal recessive, 2X-L dominant]. The most frequent were Russell-Silver, Noonan and Seckel syndrome (Tables 1,2).

Twenty eight cases (23.3%) had systemic diseases; 16 had mucopolysaccharidosis, 10 had haemoglobinopathies (7β thalassemia and 3 seckle cell anemia) and 2 had hypophosphatemic rickets. (Table 1). Patients with hypophosphatemic rickets were diagnosed early because of a positive family history, hypophosphatemia and elevated serum alkaline phosphatase with normocalcemia.

Twenty four cases (20%) had chromosomal abnormalities (22 females and 2 males). All females cases had Turner syndrome, i.e. 25.3% (22/87) of the studied females had Turner syndrome (either classical, variant or mosaic). The most frequent karyotype was 45, X detected in 10 cases. Other cases had mosaicism and structural abnormalities of the X-chromosome. Two males had chromosomal aberrations; one had 47, XXY and GHD, the other had deletion of short arm of chromosome 18 with panhypopituitarism. (Tables 1,3). Increased chromosomal breaks was detected in patients with fanconi anemia, and defective DNA repair after UV exposure was demonstrated in patients with De-Sanctis Cacchione syndrome.

Twenty cases (16.7%) had endocrine disorders. Ten had growth hormone deficiency [Isolated GHD (8) and panhypopituitarism (2)], three had GH insensitivity syndrome and seven had congenital hypothyroidism.

Fifteen cases (12.5%) had normal growth variants; 8 had constitutional growth delay and 7 had familial short stature (Table 1).

In the present study 37.5% of the cases had positive family history of proportionate SS. The frequency of parental consanguinity was 60.4% (Table 4).

Table 1: Classification of the studied cases according to their genetic etiology.

Genetic etiology	No	%
I. Pathologic causes <<105>>		
• Syndromal disorders	33	27.5
• Systemic diseases [28]		23.3
- Mucopolysaccharidosis	16	
- Haemoglobinopathies	10	
- X-L hypophosphatemic rickets	2	
• Chromosomal disorders	24	20
• Endocrine disorders [20]		16.7
- Growth hormone deficiency	10	
- GH insensitivity syndrome	3	
- Congenital hypothyroidism	7	
II. Normal growth variants <<15>>		12.5
- Constitutional growth delay	8	
- Familial short stature	7	
Total	120	100

Table 2: Distribution of cases with syndromal disorders.

Single gene disorder	No	MIM[9]*
Autosomal dominant [19]		
– Russell-Silver syndrome	7	*180 860
– Noonan syndrome	5	163 950
– Neurofibromatosis type 1	3	162 200
– Rubinstein-Taybi syndrome	2	180 849
– Cornelia-de lange syndrome	2	122 470
Autosomal recessive [12]		12.5
– Seckel syndrome	4	**210 600
– De-Sanctis-cacchione syndrome	2	278 800
– Wolfram syndrome [DIDMOAD]	2	222 300
– Fanconi anemia	2	227650
– Robinow syndrome	2	268 310
X-linked dominant [2]		
– Focal dermal hypoplasia	2	***305600
Total	33	

* MIM: Mckusick Inheritance in Man.
* Autosomal dominant [AD].
** Autosomal recessive [AR].
*** X-linked dominant [X-L].

Table 3: Distribution of cases according to their cytogenetic results.

Karyotype	No
Normal female	65
Abnormal female [Turner] (n=22)	
– 45,X	10
– 46,X,i(X_q)	4
– 46,XX/45,X	3
– 46,X,del (X_p)	2
– 46,XX/46,X,i(X_q) /45,X	2
– 45,X/46,X,r(X)	1
Normal male	31
Abnormal male [n=2]	
– 47,XXY	1
– 46,XY,del(18)(P_{11})	1
Total	**120**

Table 4: Distribution of cases according to parental consanguinity and family history.

Type	Family history of SS		Parental consanguinity	
	No	%	No	%
Positive	36	37.5	58	60.4
Negative	60	62.5	38	39.6
Total	*96	100	96	100

Total number after exclusion of chromosomal anomalies (24 cases).

DISCUSSION

Short stature is a common problem for children and adolescents worldwide. It may be a disability and a cause of distress in itself. Therefore, SS is important and require early assessment[2,9]. A sensitive screening system and an effective referral channel to genetic centers are specially important in the management of SS.[9]

In the present study, the female to male ratio was 2.6:1. Previous studies reported similar findings[10,11] this is due to the high index of suspicious of Turner syndrome and the awareness of the importance of its early recognition and treatment.

In the present study, 105 (87.5%) cases had genetic pathological conditions and 15 (12.5%) had normal growth variants. Several previous studies reported a higher frequency of normal growth variants ranging from 32% to 47%.[1,12] The high frequency of genetic pathological conditions in the present study is due to the fact that most of the referred cases to our genetic unit had genetic and/or inherited disorders.

There is a wide variety of fetal malformation syndromes associated with proportionate SS, caused by single gene disorders. Although in most cases, the causes are obscure, a specific diagnosis of a recognizable syndrome usually can be made.[5]

Previous studies reported syndromal disorders as an important cause of pathologic SS[2,5]. In the present study, sydnromal disorders were diagnosed in 33 cases. The most frequent were Russell-Silver syndrome. Noonan Syndrome and Seckel syndrome. This is in agreement with previous studies.[4,10]

Many fetal malformation syndromes with proportionate SS are inherited as autosomal recessive traits[5]. In this study, 12 cases had AR syndromes [Seckel syndrome, De-sanctis Cacchione syndrome, Wolfram syndrome, Fanconi anemia and Robinow syndrome]. The presence of affected sibs together with parental consanguinity in eight cases

supported AR inheritance. Robinow syndrome is genetically heterogenous condition. The detection of rib fusions in the studied cases confirm the diagnosis of autosomal recessive variant.[13]

In the present study, increased chromosomal breaks was detected in 2 cases with Fanconi anemia, and defective DNA repair after UV exposure was demonstrated in another 2 cases with De-Sanctis Cacchione Syndrome. This confirmed their diagnosis. This is previously reported.[14,15]

Other fetal malformation syndromes with proportionate SS usually occur sporadically such as Russell-Silver Syndrome, Cornelia de-lange syndrome and Rubinstein-Taybi syndrome, due to new mutation or submicroscopic chromosomal deletion[5,16]. In this study, 11 cases had Russell-Silver, Conelia delange and Rubinstein-Taybi syndrome. Negative family history in all these cases suggests new mutation.

Some malformation syndromes with proportionate SS are inherited as autosomal dominant trait[5]. In this study, 3 cases had neurofibromatosis type I and 5 cases had Noonan Syndrome. This has been previously reported[17,18]. Careful clinical examination of their parents revealed affected parents in 4 cases, confirming AD inheritance, necessitating genetic counseling and prenatal diagnosis. Two studied cases had focal dermal hypoplasia, which is an X-L dominant trait[19]. An effective multidisciplinary intervention can improve the quality of life in these cases.

Although, most autosomal abnormalities and syndromal disorders are not treatable in terms of final height, a definitive diagnosis modifies the management plan for the patient and indicates psychological and genetic counseling for the family[5,10]. Growth hormone therapy in children with some malformation syndromes e.g. Russell-Silver Syndrome and Noonan Syndrome improves final height.[16,18,20]

Many previous studies reported systemic diseases as a pathologic cause of SS[2,3] Sixteen cases in this study had mucopolysaccharidosis. (MPS). Short stature in MPS is most probably due to growth hormone deficiency, low insulin-like growth factor-1 and/or hypothyroidism[21]. Enzyme replacement and hematopioetic stem cell transplantation are used to treat children with MPS.[21,22]

Short stature is a frequent clinical picture in haemoglobinopathices most probably due to dysfunction of growth hormone-insulin like growth factor-I axis[23,24]. In the present study, 7 patients had thalassemia major and 3 had sickle cell anemia. Recombinant growth hormone therapy improves growth velocity, heart function and bone mineral density in thalassemic patients[23]. Two studied cases had X-L hypophosphatemic rickets. X-L hypophosphatemic patients present with disproportionate SS and bone deformities of the lower limbs[25]. The cases detected in this study were early diagnosed, before development of bone deformities, because of the presence of similarly affected sibs. Treatment with Vit D metabolites combined with inorganic phosphate salts improve linear growth as well as healing rickets in some patients.[25]

In the present study, 24 cases (20%) had chromosomal anomalies. Turner syndrome represented 25.3% (22/87) of the studied females. The most frequent Karyotype was 45, X detected in 10 cas-

es, other cases had mosaicim and structurial abnormalities of the X-chromosome. Previous studies revealed similar findings[10,11,26] some girls with Turner syndrome especially those with mosaicism express few phenotypic features prepubertally except for SS. Therefore, all girls with unexplained SS have to be referred for genetic evaluation and chromosomal studies. In Turner syndrome, introducing growth hormone for SS in early childhood and osterogen by adolescence for pubertal development and prevention of osteoporosis is very important.[27,28]

In the present study, 2 males had chromosomal anomalies. Moreno-Garcia et al reported a low frequency of chromosomal anomalies among males with SS[11]. One male had Klinfelter syndrome and growth hormone deficiency. This is previously reported by Reinehr et al.[29] The other male had deletion of short arm of chromosome 18 together with panhypopituitarism. This chromosomal anamoly was previously reported with a single maxillary incisor suggesting that the associated pituitary insufficiency may be due to hypothalamic defects[5]. This indicates the needs for cytogenetic study in all children with proportionate SS.

Many disturbances in the endocrine system can impair linear growth[1,2]. In the present study. Twenty cases (16.7%) had endocrine disorders. The commonest was growth hormone deficiency (GHD). This is in agreement with previous studies[1,3,30]. In the present study, 10 cases had GHD [8 had isolated GHD, 2 had panhypopituitarism] and 3 had GH resistance syndrome. The basic defect in GH resistance syndrome is abnormal or deficient GH receptors[31]. Referral to a pediatric endocrinologist may be appropriate as GH replacement is necessary. Congenital hypothyroidism is one of the most common preventable causes of mental retardation[32]. In the present study, 7 cases had congenital hypothyroidism, four of them had parental consanguinity and affected sibs. This is most probably due to an autosomal recessive inborn error in thyroid hormone synthesis. Newborn screening programme is important to allow early detection and treatment.[32]

In the present study, normal growth variants were diagnosed in 15 cases (8 had constitutional growth delay and 7 had familial SS). All had positive family history of SS and/or delayed puberty. In adolescent with constitutional growth delay, and severe psychological distress, hormone therapy to accelerate puberty may be appropriate[33]. Careful clinical examination of parents in cases suggestive of familial SS is very important because some of the pathological causes of SS are inheritable.

In the present study, 60.4% of the cases had consanguineous parents, which is higher than the general population (28.9%)[34]. The association of parental consanguinity and genetic disorders was proved in previous studies[1,35]. This could explain the presence of different inheritable disorders with proportionate SS in this study. Genetic counseling is highly recommended in these families.

CONCLUSION

This study highlighted the genetic etiologies of proportionate SS. Syndromal disorders, systemic diseases and chromosomal disorders are the most frequent genetic causes of proportionate SS in Alexandria, Egypt. Increased parental consanguinity and positive family

history in cases with SS necessitate genetic counseling to the public. Careful clinical examination of parents in cases suggestive of familial SS is very important. Chromosomal analysis should be done to all girls with unexplained SS. Genetic evaluation of cases with SS is necessary to reach accurate diagnosis allowing proper management and genetic counseling to the patient and his family. A collaborative study to acertain all causes of SS in the general population should be performed in order to delineate the complete picture in short stature of children living in Egypt.

REFERENCES

1. Moayeri H, Aghighi Y. A prospective study of etiology of short stature in 426 short children and adolescents. Arch. Iranian Med. 2004; 7 (1): 23-7.

2. Simm PJ, Werther GA. Child and adolescent growth disorders--an overview. Aust.Fam.Physician 2005; 34 (9): 731-7.

3. Desai MP. Growth disorders. MJAFI 2003; 59 (4): 278-82.

4. Randeva HS. Evaluation of short stature. BMJ 2006; 8:131-74.

5. Rimoin DL, Connor JM, Pyeritz RE, Korf BR. Emery and Rimoin's principles and practice of medical genetics. 5th ed.: Churchill Livingstone; 2007.

6. Weiner JS, Lourie JA. Human biology: A guide to field methods. I.B.P. Handbook. Oxford and Edinburgh: Blackwell Scientific Publications; 1969.

7. El-Ruby M, Ismail S, Salem S, Ghaly I. Genetic and anthropometric study in short stature. University of Alexandria; 1986.

8. Sharma AK, Sharma A. Chromosome analysis following short and long cultures in animals, including man. In: Sharma AK, Sharma A, editors. Chromosome techniques. 3rd ed.: Butterworth-Heinemann Ltd.; 1980. p. 361-2.

9. McKusick VA. Mendelian inheritance in man, catalogues of autosomal dominant, autosomal recessive and X-linked phenotypes. Johns Hopkins University Press; 1995.

10. Lam WF, Hau WL, Lam TS. Evaluation of referrals for genetic investigation of short stature in Hong Kong. Chin. Med.J.(Engl) 2002; 115 (4): 607-11.

11. Moreno Garcia M, Fernandez Martinez FJ, Barreiro Miranda E. Chromosomal anomalies in patients with short stature. Pediatr.Int. 2005; 47 (5): 546-9.

12. Colaco P, Desai M. Identification of a child with short stature. Indian Pediatr. 1990; 27 (11): 1159-64.

13. Mazzeu JF, Pardono E, Vianna Morgante AM, Richieri Costa A, Ae Kim C, Brunoni D, et al. Clinical characterization of autosomal dominant and recessive variants of Robinow syndrome. Am.J.Med. Genet.A. 2007 15; 143 (4): 320-5.

14. Giri N, Batista DL, Alter BP, Stratakis CA. Endocrine abnormalities in patients with Fanconi anemia. J.Clin. Endocrinol.Metab. 2007; 92 (7): 2624-31.

15. Roson E, Garcia Doval I, de la Torre C, Feal C, Cruces M. Sindrome de De

Sanctis-Cacchione. [De Sanctis-Cacchione syndrome]. Actas Dermosifiliogr. 2005; 96 (9): 586-8.

16. Prins T, Fodor M, Delemarre van de Waal,H.A. Pituitary mRNA expression of the growth hormone axis in the 1-year-old intrauterine growth restricted rat. J. Neuroendocrinol. 2006; 18 (8): 611-20.

17. Alwan S, Armstrong L, Joe H, Birch PH, Szudek J, Friedman JM. Associations of osseous abnormalities in Neurofibromatosis 1. Am.J. Med. Genet. A. 2007 15; 143 (12): 1326-33.

18. Noordam K. Expanding the genetic spectrum of Noonan syndrome. Horm. Res. 2007; 68 Suppl 5: 24-7.

19. Maymi MA, Martin Garcia RF. Focal dermal hypoplasia with unusual cutaneous features. Pediatr. Dermatol. 2007; 24 (4): 387-90.

20. Hintz RL.Growth hormone:Uses and abuses. BMJ 2004 17; 328 (7445): 907-8.

21. Polgreen LE, Tolar J, Plog M, Himes JH, Orchard PJ, Whitley CB, et al. Growth and endocrine function in patients with Hurler syndrome after hematopoietic stem cell transplantation. Bone Marrow Transplant. 2008; 41 (12): 1005-11.

22. Byers S, Nuttall JD, Crawley AC, Hopwood JJ, Smith K, Fazzalari NL. Effect of enzyme replacement therapy on bone formation in a feline model of mucopolysaccharidosis type VI. Bone 1997; 21 (5): 425-31.

23. La Rosa C, De Sanctis V, Mangiagli A, Mancuso M, Guardabasso V, Galati MC, et al. Growth hormone secretion in adult patients with thalassaemia. Clin.Endocrinol.(Oxf) 2005; 62 (6): 667-71.

24. Collett Solberg PF, Fleenor D, Schultz WH, Ware RE. Short stature in children with sickle cell anemia correlates with alterations in the IGF-I axis. J.Pediatr.Endocrinol.Metab. 2007; 20 (2): 211-8.

25. Makitie O, Doria A, Kooh SW, Cole WG, Daneman A, Sochett E. Early treatment improves growth and biochemical and radiographic outcome in X-linked hypophosphatemic rickets. J.Clin.Endocrinol.Metab. 2003; 88 (8): 3591-7.

26. Catovic A. Cytogenetics findings at Turner syndrome and their correlation with clinical findings. Bosn J.Basic Med.Sci. 2005; 5 (3): 54-8.

27. Morgan T. Turner syndrome: Diagnosis and management. Am.Fam.Physician 2007 1;76 (3): 405-10.

28. Krysiak R, Gdula Dymek A, Bednarska Czerwinska A, Okopien B. Growth hormone therapy in children and adults. Pharmacol.Rep. 2007; 59 (5): 500-16.

29. Reinehr T, Hinney A, de Sousa G, Austrup F, Hebebrand J, Andler W. Definable somatic disorders in overweight children and adolescents. J.Pediatr. 2007; 150 (6): 618,22, 622.e1-5.

30. Awan TM, Sattar A, Khattak EG. Frequency of growth hormone deficiency in short statured children. J.Coll.Physicians Surg.Pak. 2005; 15 (5): 295-8.

31. Awan TM, Sattar A, Khattak IG. High growth hormone levels in clinically

short stature children. J.Ayub Med. Coll.Abbottabad 2006; 18 (2):29-33.

32. Park SM, Chatterjee VK. Genetics of congenital hypothyroidism. J.Med. Genet. 2005; 42 (5): 379-89.

33. Iftikhar R, Akhtar J. Delayed puberty and short stature in an adolescent. Med. Today 2005; 3 (4): 177-81.

34. Hafez M, El Tahan H, Awadalla M, El Khayat H, Abdel Gafar A, Ghoneim M. Consanguineous matings in the Egyptian population. J.Med. Genet. 1983; 20 (1): 58-60.

35. Abd El Aziz AM, Mokhtar MM, Behery AK, Hassanein NM. Premarital genetic investigations; An attempt to reduce genetic disorders. Bull.High Inst. Publ.Health 2002; 32 (3): 651-64.