Growth Disorders

Dr Meena P Desai

MJAFI 2003; 59 : 278-282

Growth and development constitute the most unique and distinctive features of a child's life. The phenomenal pace of progress in the past few decades in biological sciences and biology of growth at molecular, cellular and tissue levels as well as unravelling of the mechanisms which govern this physical and maturational process, have contributed a great deal to our understanding of the pathophysiology of growth disorders. The genetic revolution is re-inventing medicine. Molecular genetic techniques have clarified the etiology of several growth disorders. Effective and regulated expression of the growth hormone (GH) pathway is essential for growth in stature as well as metabolic homeostasis. The series of interdependent genes along the GH pathway whose products are required for normal growth, their cellular receptors, GH related transcription factors and the functioning of the hypothalamic-GH-IGF-1-chondro-osseous axis have all been identified [1]. India has a unique unexplored gene pool and our experience with GH deficiency in childhood suggests that our patients with familial and the so called idiopathic GHD have identifiable genetic abnormalities leading to short stature [2]. Genetic abnormalities leading to skeletal dysplasias eg. fibroblast growth factor receptor in achondroplasia or gene deletions and aberrations in some of the dysmorphic syndromes and metabolic disorders with short stature, have also been recognised. Much information is now available on short stature homeobox containing gene (SHOX) involved in dyschondrosteosis, possibly Turner syndrome and idiopathic short stature (ISS) [3,4]. These advances in knowledge have been quickly translated into diagnostic tools, which have made the diagnosis of growth disorders more precise.

The process of growth being most vulnerable to the effects of chronic diseases, nutritional and psychosocial deprivation and adverse environmental conditions, constitutes one of the most sensitive parameters of a child's health. The only measurement of good health in the past was survival, when the primary concern of the 'Science of Child Health' was preservation of life [5].

Interestingly the credit for the first complete and extensive study of the physical growth of children goes to the Belgian astronomer and statistician Lambert Quetelet (1796-1874) [5]. Interest in physical growth and development began in early part of the 20th century with the change in approach to children's health. This led to the establishment of several research centres for cross sectional and longitudinal study of growth and development, both in America and Europe.

Appreciation of some of the central issues pertaining to normal growth and its regulation is helpful in understanding aberrations of growth. Growth is regarded as the sum total of all cell replication and tissue and organ system differentiation [5]. Stated simply, it implies increase in physical size measured by auxologic parameters and in terms of metabolic balance. Cell size plays a role, but the rate of cellular division probably governed by humoral substances or other factors, determines the cell number and hence the overall growth in size [6]. At critical periods of rapid increase in cell number, growth remains most susceptible to adverse effects [5,6]. Thus, brain is highly vulnerable during fetal life and early infancy (eg. thyroid deprivation) whereas the skeletal system is vulnerable both during this phase and throughout childhood and adolescence.

The most spectacular genetic effects are believed to be manifest in anthropologic characteristics [6]. Several genes exerting a simple cumulative action are involved in the regulation of height. Growth is also regulated by a complex interaction of hormonal influences, tissue responsiveness, nutrition, psychosocial and environmental factors which exert a powerful influence on the growing child, contributing positively to the fulfilment of the genetic plan or hinder it [6]. Secular changes in growth have occurred during the last century in almost all industrialized countries involving body size, tempo of growth and onset of puberty, as evidenced by advancement of age at menarche and peak height velocity. As prevailing conditions in society are mirrored in the growth of its children, secular changes in growth and tempo of growth often indicate the changing

nutritional, hygienic, socioeconomic and health status of a population. There are ethnic and countrywide differences in stature, hence normal reference values for assessment of growth are essential for various population groups. It is difficult to isolate genetic and environmental components completely and minor genetic differences in growth potential of population cannot be entirely ruled out. This secular trend has plateaued in many affluent nations suggesting the full realisation of genetic potential but is still to be realised in underdeveloped countries.

Genetic factors influence all cells of the body but their influence is most pronounced, an estimated 25% of the total regulatory influence on the development of skeleton and chronologic sequence of ossification [4]. Karlberg et al have proposed a mathematical model of the phases of human growth - the infancy - childhood - puberty or ICP model [7,8]. The infancy component begins from midgestation lasting till 2-3 postnatal years. This phase of rapid growth is related to nutrition which emphasizes the role of maternal nutrition in the growing fetus and the importance of sufficient nutrition in infancy for adequate growth. Nutritional deprivation during this phase of life can lead to irreversible damage and alter the genetic growth potential. The childhood component is mainly regulated by hormonal influences such as that of thyroid and GH which are important for postnatal growth but do not impair fetal growth and hence newborns with congenital hypothyroidism or GH deficiency, do not exhibit any linear growth failure at birth. The pubertal phase of growth is superimposed on the decelerating childhood component and influenced by gonadal steroids and their enhancing effect on GH-IGF-1 secretion, thyroid hormones, androgens, and other growth promoting hormones. However, as growth is a complex interplay of many factors, this oversimplified mathematical model may not be adequate to explain all its aspects.

Any discussion on 'Growth Disorders' involves both the growth deficiency disorders as well as those where growth is excessive. 'Growth Retardation' is much more frequently encountered and will be the focus of discussion in this column. Short stature is a common problem confronting the paediatrician and often the commonest cause for referral of children to endocrine services, in our experience nearly 42% of all referrals. An estimate of stunted children in developing countries gives a tentative prevalence of about 40% in children under five years, a total of about 125 million, with a general increase in prevalence with age [9,10].

As stated earlier, linear growth is the net expression of the genetic make up, adequacy of nutrition and environment and the residual effects of previous and /

or persisting disease. Amongst children with short stature relatively few are pathologically small in the context of the family and the ethnic background. In developing countries the superimposed adverse effects of various environmental factors often complicates growth retardation of endogenous origin. Growth retardation caused by primary nutritional deficiency is mainly a problem faced in the third world countries with a prevalence as high as 50% in children under five years of age, often associated with recurrent and chronic infections [9]. Biologically it has been looked upon as a useful adaptation when food is in short supply.

There is no universally accepted definition of a pathologically short individual. Short stature is defined as a height less than two standard deviation of the mean for age or below the third percentile for height on national standards for that population. However, if the child is significantly below the midparental or target height or consistently having a poor growth velocity below the 25th percentile, he/she needs careful evaluation for growth retardation.

Growth is assessed at one point in time and compared to standards for that age. It also needs to be evaluated over a period of time as the rate per unit time, or velocity of growth. Velocity of growth is equivalent to a bioassay and if normal for age will obviate the need for unnecessary investigations. Length is usually measured during the first 2 years of life with height measurements obtained beyond this age. Accurate measurements are a must. Small inaccuracies in linear stature can get magnified in determination of annual growth velocity. Most standard paediatric texts describe the manner in which length/height is obtained as well as the methodology for obtaining other standard measurements and body proportions. Precise measuring devices have been designed. In case, measure tape is used, it should be of non-stretchable sturdy material. National Centre for Health Statistics (NCHS-USA) percentile growth charts can be used for international reference, national charts, such as Agarwal's [11,12], are more relevant for routine clinical use in Indian children. Disease specific growth charts have also been developed (e.g. Turner Syndrome and achondroplasia). Standard deviation scores or z scores for comparison of various parameters are also very useful. Analysis of the relationship between chronologic age, height age (age at which the individual's height is at 50th percentile) growth velocity, midparent correlation of child's height and bone age are most helpful in evaluation of a short child. Determination of body proportions provide additional information and the most widely used are the ratio of upper to lower body segments and the relationship between arm span and height.

As multitude of factors can lead to growth deficiency, it is important to decide whether a child's small size represents only a normal variation or indicates the presence of an underlying disease. In a population of children, 2 standard deviation (SD) or 3rd percentile below the mean for height about 20%, may be expected to have pathologic short stature with the remaining 80% equally divided between familial short stature and constitutional growth delay [13]. However, most children below 3 SD have pathologic short stature.

The evolving biologic patterns of linear growth and skeletal maturation vary in differing forms of growth retardation [14]. It can be categorized as (i) intrinsic shortness which refers to primary disturbances of skeletal growth, (ii) delayed growth, refers to maturation as well as growth delay as with constitutional delay of growth and sexual maturation (CDGM), where ultimately normal stature is achieved, and (iii) attenuated growth, where normal growth can usually be achieved if underlying cause is treated before it is too late [14-16]. Thus, growth retardation of a primary nature is said to exist when there is an intrinsic defect in the skeletal system of genetic origin or prenatal damage. Skeletal dysplasias, chromosomal and genetic short stature, intrauterine growth retardation (IUGR), dysmorphic syndromes and some of the metabolic disorders belong to this category [14-16]. In most instances, growth deficiency begins before birth and the outlook for adult height is poor. The potential for bone growth is impaired but the skeletal age is usually less affected than the height age. In secondary forms of growth deficiency, extrinsic and acquired factors like nutritional, chronic infections, or systemic, metabolic and endocrine disorders, delay in osseous growth and maturation with skeletal and height age affected to a similar extent except in hypothyroidism and occasionally in GH deficiency. The potential for reaching adult height is usually retained and often achieved with early appropriate therapy [14-16].

A routine survey of 2500 hospitalised children revealed that in 60% of children with height below 5th percentile, protein energy malnutrition, long standing anaemia and chronic infections were the underlying causes for growth retardation with specific disorders or endocrinopathies in less than 10% [17]. As against this, with referrals to our endocrine service primarily for short stature, endocrinopathies were noted in 38%, normal variant short stature including familial and constitutional delay in 32%, and PEM and chronic disease in less than 10%. IUGR with its high incidence in our country was noted in 10% and skeletal disorders and dysmorphic syndromes together in another 10% [18]. The experience at the four paediatric endocrine services (AIIMS,

SGPGI, Srinagar and Vellore) in India, is similar (personal communication). Thus, causes differ significantly with the kind of child population under survey and also whether the short stature is the primary concern and reason for referral or is incidental.

Detailed history, family history and careful clinical examination, coupled with routine investigations and bone age evaluation, will elucidate the cause in a large majority of children. While a child's position on the growth curve indicates the degree of height deficit, a look at the skeletal maturation tells us about the potential for further growth. Hormonal evaluation, chromosomal studies and other sophisticated investigations like molecular genetic studies are more often needed to confirm the suspected clinical diagnosis and in children with clinical indicators of specific disorders. A possibility of Turner Syndrome cannot be ruled out in girls with significant short stature even in absence of any specific physical signs. In general, patients with disproportionate short stature have skeletal dysplasia or long standing early onset hypothyroidism. Children with nonskeletal defects, nutritional, prenatal causes, other endocrinopathies and chronic diseases have relatively normal body proportions. As previous growth records are rarely available, linear growth velocity over the ensuing 6 to 12 months in children where there is no clear indication of the underlying disorder is helpful. In a short child when the height is more than 3 SD below the mean, growth rate less than 4 cm/year, bone age retardation of more than two to three years as compared to chronologic age or clinical evidence of specific disease, immediate investigative work up needs to be undertaken.

The management of 'Growth Deficiency Disorders' varies with the underlying cause. As the causes are numerous, the management strategies vary from growth monitoring and periodic evaluation with reassurance and no treatment as with physiological variants such as familial or genetic short stature (FSS) CDGM, to active specific therapy of the underlying disease, or the use of growth promoting agents. Nutritional and psychosocial support are important. In a condition such as FSS, parents need to understand and emphasize other achievements of the child instead of focusing on stature so that his/her self esteem does not suffer. All forms of vigorous exercise should be encouraged and are beneficial for a variety of reasons but none is meant specifically to improve height. Balanced diet with recommended allowances is advisable. Boys with CDGM are often emotionally disturbed because of delayed sexual maturation. If reassurance does not suffice, cautious use of short term therapy with anabolic steroids or testosterone is recommended to activate the dormant hypothalamic-pituitary-gonadal axis. Other

systemic disorders require disease appropriate management. Adequate calories, proteins and nutritional supplements with vitamins, iron, other minerals, are advocated.

Availability of recombinant biosynthetic growth hormone since mid 80s in large and unrestricted amounts, has also multiplied the indications for its use to improve height [19,20]. It is a powerful and potent hormone for promoting growth and increasing the growth rate in any short child with open epiphyses during initial phase of 12 to 24 months of its use, but the ultimate and long term benefit for height is questionable. The effect is most remarkable and is extremely beneficial in children with proven growth hormone deficiency and also in a proportion of girls with Turner syndrome [19,20]. It is recommended in children with chronic renal insufficiency who are short, along with appropriate management of the metabolic alterations. It is under trial and considered investigational in children with hypochondroplasia, specific syndromes such as Prader Willi and Roussel Silver and in other forms of IUGR [19,20]. Experimental and clinical data also support the role of GH therapy in children on long term glucocorticoid treatment both as a growth promoting and an anabolic agent, specifically to prevent protein wasting and osteopenia. Controversies still surround its use in short normal children and children categorized as having idiopathic short stature [20]. Some of the recent studies suggest a modest increase in final height to the extent of 3-4 cm compared to untreated controls, and some benefit in achieving target height in a significant proportion of cases. However, more data is necessary. Potential adverse effects during therapy need monitoring and long term after effects need to be studied.

Limb lengthening external fixator surgical techniques of Ilizarov have been used for skeletal dysplasias such as achondroplasia. These are invasive, cumbersome and may take 2 to 4 years with long periods of hospital stay. Height increments of 7 to 14 cm may be possible.

The 'Science of Growth' as it relates to growth and its pathophysiology at cellular and molecular levels deals with the mystery of life. New diagnostic tools such as PCR and molecular probes help the clinician achieve a precise diagnosis of the underlying disorder. Whether equivalent degree of therapeutic success can be obtained with genetic engineering, recombinant DNA technology and newly acquired biosynthetic capabilities, is to be seen. Discovery of new molecules and pharmaceutical compounds often raise new concerns. The goal and the very essence of Preventive Medicine in children is promotion of normal growth and development. There is continuing debate whether short non-GHD children suffer psychological stress and hence

should be administered GH [21]. Health is often quoted as being a state of complete physical, mental, emotional and social well being. Others argue that the proper aim of healthcare should be prevention or cure of identifiable diseases and disabilities. Thus it can also be argued that GH therapy of children with normal short stature tantamounts to labelling a normal physiological variation of stature as a disorder requiring treatment. Is it justified? Will this result in offering therapy to the present as well as future generations of short children? These are some of the ethical and socioeconomic issues which need to be addressed and discussed but probably never be resolved.

References

1. Cogan JD, Phillips JA. Growth disorders caused by genetic Defects in the Growth Hormone pathway. *Advances in Paediatrics* 1998;45:337-61.
2. Desai MP, Ogawa M, Yamamoto M et al. Growth Hormone Releasing Hormone Receptor (GHRH-R) gene mutation in familial Growth Hormone deficiency. *J Pediatr Endo & Metab* 2000;13:Suppl 3:1170.
3. Rao E, Weiss B, Fukami M et al. Pseudoautosomal/deletions encompassing a novel homeobox gene cause growth failure in idiopathic short stature and Turner syndrome. *Nat Genet* 1997;16:54-63.
4. Belin V. SHOX mutations in dyschondroosteosis Leri-Weill Syndrome. *Nat Genet* 1998;19:67-9.
5. Lowrey GH. History and Introduction. In : Lowrey GH, editor, *Growth & Development of Children*. 7th ed 1978 Year Book Medical Publishers, Chicago.
6. Smith DW. *Growth and its Disorders : Major problems in clinical paediatrics*. 15th ed 1977, Philadelphia, WB Saunders.
7. Karlberg J, Engstrom I, Karlberg P, Fryer JG. Analysis of linear growth using a mathematical model I from birth to three years. *Acta Paediatr Scand*, 1987;76:478-88.
8. Karlberg J, Fryer JG, Engstrom I, Karlberg P. Analysis of linear growth using a mathematical model II from 3 to 21 years of age. *Acta Paediatr Scand* 1987;Suppl 337:12-29.
9. Waterlow JC. Nutritional effects on growth. In: Brusner O, Carazza FR, Gracey M et al editors, *Clinical nutrition of the young child*, Nestle Nutrition. Raven Press, New York 1985.
10. Keller W. The epidemiology of stunting in Linear Growth Retardation in less developed countries. 14th Nestle Nutrition Workshop, 1986.
11. Agarwal DK, Agarwal KN. Physical growth of Affluent Indian Children (birth to 6 years) *Indian Paediatrics* 1994;31:377-413.
12. Agarwal DK, Agarwal KN, Upadhyay SK et al. Physical and sexual growth pattern of affluent Indian children for 5 to 18 years of age. *Indian Paediatrics* 1992;29:1203-68.
13. Mahoney CP. Evaluating the child with short stature. *Paediatrics Clin N Am* 1987;34:825-49.
14. Rimoin DL, Horton WA. Short Stature Part I. *J Pediatr* 1978;92:523.
15. Rimoin DL, Horton WA. Short Stature Part II, *J Pediatr* 1979;92:697.

16. Schaft-Blass E, Burstein S, Rosenfield RL. Advances in the diagnosis and treatment of short stature with special reference to the role of growth hormone. *J Pediatr* 1984; 104:801-3.
17. Colaco MP, Vichare PA, Desai MP, Samuel AM. Evaluation of growth retardation : Etiologic factors. *Ped Clin of India*, 1984;19:17-24.
18. Colaco P, Desai M. Identification of a child with Short Stature. *Indian Pediatrics* 1990;27:1159-64.
19. Committee on Drugs and Committee on Bioethics : Consideration related to the use of recombinant human growth hormone in children. *Pediatr* 1997;99:122.
20. Guidelines for the use of growth hormone in children with Short Stature. A report by the Drug and Therapeutics Committee of the Lawson Wilkins Paediatric Endocrine Society. *J Pediatr* 1995;127:857.
21. Haverkamp F, Noeker M. Short Stature in children - a questionnaire for parents : a new instrument for growth disorder - specific psychosocial adaptation in children. *Qual Life Res* 1998;7:447-55.

ATTENTION CME ORGANISERS

All service hospitals/institutions organising CME will contribute to MJAFI fund as per rates given below :-

(a) CME with less than 100 delegates	- Rs. 2500/-
(b) CME upto 300 delegates	- Rs. 5000/-
(c) CME with more than 300 delegates	- Rs. 10000/-