Clinical Rounds in Endocrinology

Volume II
Pediatric Endocrinology

Anil Bhansali
Anuradha Aggarwal
Girish Parthan
Yashpal Gogate

Springer

Clinical Rounds in Endocrinology

Anil Bhansali • Anuradha Aggarwal
Girish Parthan • Yashpal Gogate

Clinical Rounds in Endocrinology

Volume II - Pediatric Endocrinology

Springer

Anil Bhansali
Professor and Head
Department of Endocrinology
Postgraduate Institute of Medical
Education and Research
Chandigarh
India

Anuradha Aggarwal
Consultant
Paras Hospital
Patna
India

Girish Parthan
Consultant
Renal Medicity
Cochin
India

Yashpal Gogate
Consultant
Harmony Health Hub
Nasik
India

ISBN 978-81-322-2813-4 ISBN 978-81-322-2815-8 (eBook)
DOI 10.1007/978-81-322-2815-8

Library of Congress Control Number: 2015942899

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer (India) Pvt. Ltd.

Dedicated
to
My beloved mother late Shrimati Munna Kumari Bhansali,
the inspiring force in my life
My father Shri ML Bhansali, the guiding light
of my life
My wife Sandhya, my pillar of strength who always
stood by me and
My loving children Shipra, Shobhit, and Akanksha

Anil Bhansali

Foreword

I feel humbled to take this opportunity to introduce the text that follows, which I am confident, will prove to be a cerebral feast for the readers. I know Dr. Bhansali as an astute clinician and dedicated academician and have expected his textbook to be a perfect combination of theory and practical medicine. I am glad that this textbook has stood up to the expectation.

This textbook covers all the significant disorders commonly encountered in pediatric endocrinology practice in 12 chapters, which include first two chapters on growth disorders followed by one chapter each on thyroid disorders, Cushing's syndrome, delayed and precocious puberty, Turner syndrome, rickets, congenital adrenal hyperplasia (CAH), disorders of sex development (DSD), and young diabetes and multiple endocrine neoplasia syndromes. Each chapter begins with a clinical case vignette followed by detailed description of the topic, presented as answers to questions of clinical relevance.

I feel the details covered in case vignette represents the proverbial "Well begun is half done." The cases are replete with complete details about clinical features, examination, diagnosis, and management. However, the outstanding feature is the discussion of differential diagnosis, with pertinent arguments for and against each differential, which will immediately make both the practicing endocrinologists and trainees to feel familiar with the essential logical navigation. I am sure; it would definitely enhance their clinical approach to these disorders.

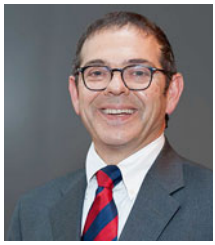
The patients' photographs are well representative and give a lively clinical experience to readers. The discussion of the topic is enriched with well-illustrated diagrams and informative algorithmic flowcharts. Moreover, the underlying physiology is explained at such places that relevance of clinical findings is enhanced. The contrasting features in related disorders are brought out well in tabulated forms for easy understanding. To name a few, there are good tables comparing features of different growth charts, merits and demerits of different GH stimulation tests, and differential features of various DSDs. Most importantly, Indian normative references are given, for example, those on age-specific reference range for testicular volume and stretched penile length to suit the readers in Indian scenario. This text is abreast with updated information on recent developments like discussion on suitability of IAP 2015 growth charts. Practical information on certain topics like that on neonatal screening of CAH and management of CKD-MBD is particularly helpful.

On the whole, I believe this book is a "must have" for endocrine trainees and practicing pediatric endocrinologists alike. It provides a well-abridged quick referral which will certainly enhance clinical approach to pediatric endocrine disorders and benefit the patients at large.

I would like to complement and thank Dr. Bhansali and his colleagues whose relentless efforts have fructified into such a well-written book.

Nalini Shah
Professor and Head,
Department of Endocrinology,
KEM Hospital,
Mumbai, India

Foreword



It is with great pleasure that I write a foreword to this book on Pediatric Endocrinology as part of the *Clinical Rounds in Endocrinology* series. This book is comprised of an impressive series of chapters covering growth disorders, puberty, thyroid, adrenal, rickets, Turner syndrome, endocrine neoplasia, and diabetes. Adult manifestations of pediatric endocrine disorders are also covered. The structure of the chapters is unusually lively with a case vignette, a detailed stepwise analysis, and a series of short questions/answers covering physiology, pathophysiology, diagnosis, management, and treatment. Illustrative short cases are often presented as part of the chapters. The chapters are richly illustrated by patient photos, imaging, figures, tables, and decision algorithms, helping the reader to rapidly grasp the key messages. Some but not all the chapters also have pros and cons of the various treatment options, for instance management of hypogonadism at puberty. This book will be of interest to all those interested in pediatric endocrinology. For the beginner, this book escapes the traditional textbook format, but its wide series of questions covers all aspects of the topics covered and allow a comprehensive overview. For those who are already acquainted with pediatric endocrinology, this book is up to date with recent references, and I am positive that there will be something for everyone there. Dr. Anil Bhansali and his colleagues are to be commended for achieving such a comprehensive and richly illustrated book that will be of interest not only to the endocrine community in India but also in other areas of the world.

Pr Jean-Claude Carel
March 2016
University Paris Diderot, Sorbonne Paris Cité, F-75019,
Paris, France

Department of Pediatric Endocrinology and Diabetology,
and Centre de Référence des Maladies
EndocriniennesRares de la Croissance
Assistance Publique-Hôpitaux de Paris (AP-HP),
HôpitalUniversitaire Robert-Debré

Foreword

It is a pleasure to introduce this book on Pediatric Endocrinology to you. Its unique informal question-answer style sets it apart from the routine medical text. The questions asked are full of insight and reflect the years of teaching experience of the authors. Most chapters start off with a case vignette and relevant issues in pathology and physiology are woven around the cases. Management issues are taken up in great depth. Growth, puberty, and disorders of sex development, including congenital adrenal hyperplasia, the core areas of pediatric endocrinology, are covered in minute detail. Other relevant chapters include most issues of importance to those treating not only children and adolescents but also those caring for the young patient in transition to adulthood. The rich collection of patient photographs and flowcharts makes for easy clinical learning. This book will provide useful and refreshing reading for practitioners and teachers of pediatric endocrinology, endocrinology, pediatrics, and also clinical genetics and gynecology.

Vijayalakshmi Bhatia
Professor,
Department of Endocrinology,
SGPGI,
Lucknow, India

Preface

Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, is the premier medical and research institute in India. This tertiary health-care center, right from its days of inception, has always been at the forefront in the field of medical sciences. The concept of endocrinology in India was originated from this institute, and endocrinology as a super-specialty department was established way back in 1964 at this institute by Professor G.K. Rastogi.

This department has an age-old tradition of grand academic rounds. Detailed discussions pertaining to every aspect of patient's care include right from analysis of symptoms, demonstration and interpretation of signs, critical appraisal of differentials, judicious use of investigations and their appropriate analysis, and finally optimal treatment strategies. This legacy of clinical rounds was inherited from my great teacher, Professor R.J. Dash, who had in-depth and enormous knowledge of the subject with a great ability to critically analyze it. Several thought-provoking questions were spontaneously generated during these interactive sessions, with inputs and suggestions by residents and views and counter-views by the faculty members making these clinical rounds a "sea of knowledge." Further, this continuous process of exchange of knowledge helped us in providing the best possible medical care to our patients and growth of this super-specialty in India.

I had a long-cherished dream to compile these clinical rounds in text form with precise information, comprehensive knowledge, and critical analysis of the facts to facilitate the dissemination of the knowledge to endocrinologists, physicians, pediatricians, and gynecologists.

Recently, there is a paradigm shift in the pattern of the books available in endocrinology with a focus on molecular endocrinology rather than on clinical endocrinology. It was decided to write a book in the "question–answer" format as this pattern not only simulates clinical rounds, but will also help to the health-care professionals in dealing with challenges faced by them in day-to-day practice. Incidentally, books in such format are not readily available, particularly in endocrinology.

The idea of writing this book was conceived, conceptualized, and formatted by me, with utmost caution to present the scientific facts in the most comprehensive manner and was amply supported by my team of coauthors: Dr. Girish Parthan, Dr. Anuradha Aggarwal, and Dr. Yashpal Gogate. Dr. Soham Mukherjee and Dr. Mandeep Singla worked untiringly with me for the last 1 year in reviewing the literature, adding clinical images, tables, and illustrations, and finally editing the

text to make the book in its present shape. Further, the decision of adding the case vignette was strongly propounded by Soham; otherwise, this book would have been incomplete. The whole process in itself was a great learning experience.

This book on pediatric endocrinology includes 12 chapters covering disorders of the pituitary, adrenal, thyroid, parathyroid, gonads, and diabetes. Most chapters begin with a case vignette, followed by a stepwise analysis of the case including diagnosis and management, and subsequently a series of question and answers. Another salient feature of this book is a multitude of clinical images, illustrations, tables, and algorithms for better understanding of the clinical problem.

We hope this endeavor will help health-care professionals to conceptualize the subject of endocrinology and will translate into better patient management.

Anil Bhansali
Anuradha Aggarwal
Girish Parthan
Yashpal Gogate

Acknowledgements

We are grateful to all those who have helped us in accomplishment of this endeavor. It is indeed difficult to name all who have contributed to this book, though a few names with a lion's share in the completion of this mammoth task are mentioned.

We are grateful to all of our patients who have helped us in learning clinical endocrinology, for without them this book would have never been written.

I, Dr. Anil Bhansali, thank all my colleagues including Dr. Sanjay Kumar Bhadada, Dr. Pinkai Dutta, Dr. Rama Walia, Dr. Ashu Rastogi, Dr Soham Mukherjee and Dr. Naresh Sachdeva for their valuable suggestions and continuous support throughout this journey. I heartily appreciate the relentless and selfless efforts made by Dr Soham Mukherjee to accomplish this dream and without his support, this would not have been achieved.

I also sincerely appreciate the effort of my coauthors Dr. Girish, Dr. Anuradha, and Dr. Yashpal for their untiring and immense contribution in making this book in the present form. They have indeed inculcated the "soul" into it.

My sincere and heartful thanks to Dr. Mandeep Singla for his relentless support and continuous encouragement during the entire period. I thank all my other residents including Dr. Abhishek Hajela, Dr. Suja P Sukumar, Dr. Kushdev Jariyal, Dr. Vikram Shekhawat, Dr. Pawan, and Dr. Anshita for their help and encouragement. I also thank Prof. B.R. Mittal and Dr. Anish Bhattacharya from the Department of Nuclear Medicine and Dr. Chirag Ahuja from the Department of Radiodiagnosis for their suggestions and worthy contributions.

We are grateful to our family members for their continuous support and perseverance; without that it would have been impossible to fulfill this dream. I, Dr. Anil Bhansali, sincerely express my gratitude and appreciation to my wife Sandhya and my children Shobhit, Shipra, and Akanksha who have supported me throughout this long journey to accomplish this venture. I am also thankful to my all brothers, Sunil, Raj Kumar and Aniruddh, and sisters, Madhu, Manju and Menu for their wholehearted support to accomplish this work. I really admire my friends, justice Hari Pal Verma and Harish Singla, for their continuous encouragement and support. I, Dr. Anuradha, sincerely thank my husband Dr. Vaibhav for his continuous support and cooperation in writing this book. I, Dr. Girish, sincerely thank my wife Dr. Rajlakshmi Iyer who has allowed me to accomplish this work untiringly. I, Dr. Yashpal Gogate, sincerely thank my wife Dr. Ketki for her persistent encouragement.

We are also thankful to Mrs. Anjali Aggarwal and Sanjay Kumar for designing the beautiful diagrams and editing the images. We appreciate the kind help extended by Mr. Abhijeet and Mr. Paramjeet for acquisition of the clinical images. We also thank Mrs. Rama Puri, Mrs. Usha Sharma, Mr. Mahabir Singh, and Mr. Surinder Pandey for their uninterrupted assistance throughout the period of writing this book.

We are also thankful to our publisher Springer and their team members Dr. Naren Aggarwal, Mrs. Teena Bedi, and Mr. Pradeep Kumar. Without them this book would have never been in the present form.

Finally, we are thankful to the Almighty for providing the wisdom, courage, and strength to complete this endeavor and for the fulfillment of this long-cherished dream.

Anil Bhansali
Anuradha Aggarwal
Girish Parthan
Yashpal Gogate

Contents

About the Authors

Anil Bhansali Dr. Anil Bhansali is the Professor and Head of the Department of Endocrinology and Metabolism at the Postgraduate Institute of Medical Education and Research, Chandigarh, India. He has published 400 articles in indexed, peer-reviewed international and national journals of repute in the field of diabetes and endocrinology. His pioneer work on stem cell therapy in type 2 diabetes and diabetes complications, particularly in diabetic foot and diabetic retinopathy, is widely recognized. Dr. Bhansali has been the recipient of numerous awards and fellowships, prominent among these are the Fellow of Royal College of Physicians (Glasgow), Prof. M.N. Sen ICMR Award for Pituitary Disorders, Prof. M. Viswanathan Award for Stem Cell Therapy in T2DM, Prof. Shurvir Singh Award for Research in Diabetes, and Dr. P.N. Shah Memorial Award for Metabolic Bone Disease. He was the Ex-President of the Endocrine Society of India and the Founder President of the Punjab and Chandigarh Chapter of Research Society of Study of Diabetes in India.

Anuradha Aggarwal Dr. Anuradha Aggarwal did her DM from the prestigious Postgraduate Institute of Medical Education and Research, Chandigarh, India. Currently, she is working as a Consultant endocrinologist at Paras Hospital, Patna, India. She is actively involved in research activities particularly in pediatric endocrinology.

Girish Parthan Dr. Girish Parthan did his DM from the prestigious Postgraduate Institute of Medical Education and Research, Chandigarh, India. Currently, he is working as Consultant endocrinologist at Renal Medicity, Cochin, India. He has interest in diabetes, particularly in clamp studies.

Yashpal Gogate Dr. Yashpal Gogate did his DM in endocrinology from the prestigious Postgraduate Institute of Medical Education and Research, Chandigarh, India, and is currently working at Harmony Health Hub at Nashik, Maharashtra, India. He is actively involved in patient care and research and is a prolific writer.

Disorders of Growth and Development: Clinical Perspectives

1

1.1 Case Vignette

A 9-year-old boy presented with complaint of growth failure since 2 years of age. He was a product of non-consanguineous marriage and was delivered at term by normal vaginal delivery. His birth weight was 3.3 Kg and he had normal Apgar score. However, data of his birth length was not available. He had history of prolonged physiological jaundice, that lasted for 3 weeks and required phototherapy for its resolution. There was no history of any episode of hypoglycemia. His developmental milestones were normal, except delay in walking which was due to congenital dislocation of his left hip. The growth velocity data available, showed his height at 1 year of age was 65 cm, at second year 75 cm, and later at the age of 9 year it was 96 cm with annual growth velocity of approximately 3 cm/year from third year of age onward. He has good scholastic performance and now is studying in fourth standard. There was no history of any systemic illness, chronic diarrhea, drug intake (e.g., steroid), head injury, meningitis/encephalitis, headache, and visual defects. He had no history of fatigue, lethargy, irritability, somnolence, or constipation. His both parents were short and were at $<3^{rd}$ percentile. He has one sibling with normal history of growth and development. On examination, his height was 96 cm (−7 SDS, height age 3 years, target height 164 cm), upper and lower segment ratio 1.2, arm span 92 cm, weight 21.2 Kg (weight age 6 years), and BMI 23 Kg/m^2 ($>95^{th}$ percentile). He had cherubic face with frontal bossing, depressed nasal bridge, midfacial hypoplasia, low-set ears, and poor dentition with crowded teeth. He had no goiter. His blood pressure was 90/60 mmHg. He had bilateral palpable testes with testicular volume of 1 ml and stretch penile length of 2 cm with Tanner staging of A_1P_1. He had bilateral palpable testes with testicular volume of 1 ml and stretched penile length of 2 cm, and he had bilateral lipomastia. Systemic examination was unremarkable except shortening of his left lower limb with restriction of movement at the left hip joint. On investigations, his hemoglobin was 10 g/dl with normal total and differential leukocyte counts. Renal and liver function tests, electrolytes (K^+ and

A. Bhansali et al., *Clinical Rounds in Endocrinology*,
DOI 10.1007/978-81-322-2815-8_1

HCO_3^-), calcium profile, and IgA tTG were normal. Hormonal profile showed serum T_4 6.7 μg/dl (N 4.8–12.7), TSH 4.6 μIU/ml (N 0.27–4.2), 0800h cortisol 140 nmol/L (N 171–536), LH <0.1 mIU/ml (N 1.7–8.6), FSH 0.52 mIU/ml (N 1.5–12.4), testosterone <0.08 nmol/L (N 9.9–27.8), prolactin 5.07 ng/ml (N 4–15.2), and IGF1 50 ng/ml (N 58–401). GH response to insulin-induced hypoglycemia and clonidine stimulation test, after priming with estrogen, were performed and showed subnormal peak GH response to both these stimuli (<0.03 ng/ml for both). Peak cortisol response to insulin-induced hypoglycemia was also suboptimal (150 nmol/L). His bone age was 7 years. CEMRI sella showed small pituitary with normal midline stalk and eutopic posterior pituitary bright spot. X-ray pelvis showed dislocation of left hip joint. With this profile, a diagnosis of multiple pituitary hormone deficiency (GH and ACTH) was considered, and patient was initiated with rhGH at doses of 0.3 mg/Kg/week and hydrocortisone 2.5 mg twice a day. With this treatment, the growth velocity during first year was 11 cm and during second year was 14 cm, and after 2 years of initiation of rhGH therapy, the height increased from 96 to 121 cm. His weight increased from 21 to 41 Kg, possibly due to immobilization during his surgery for hip dislocation. After 3 months of initiation of rhGH, the serum T_4 level declined to 5.2 μg/dl and he was initiated with 50 μg/day of L-thyroxine. Serum IGF1 levels were 378 ng/ml (N 70–458) and 251 ng/ml (N 82–516) after first and second years of therapy, respectively. No adverse event was noted during the course of therapy (Fig. 1.1).

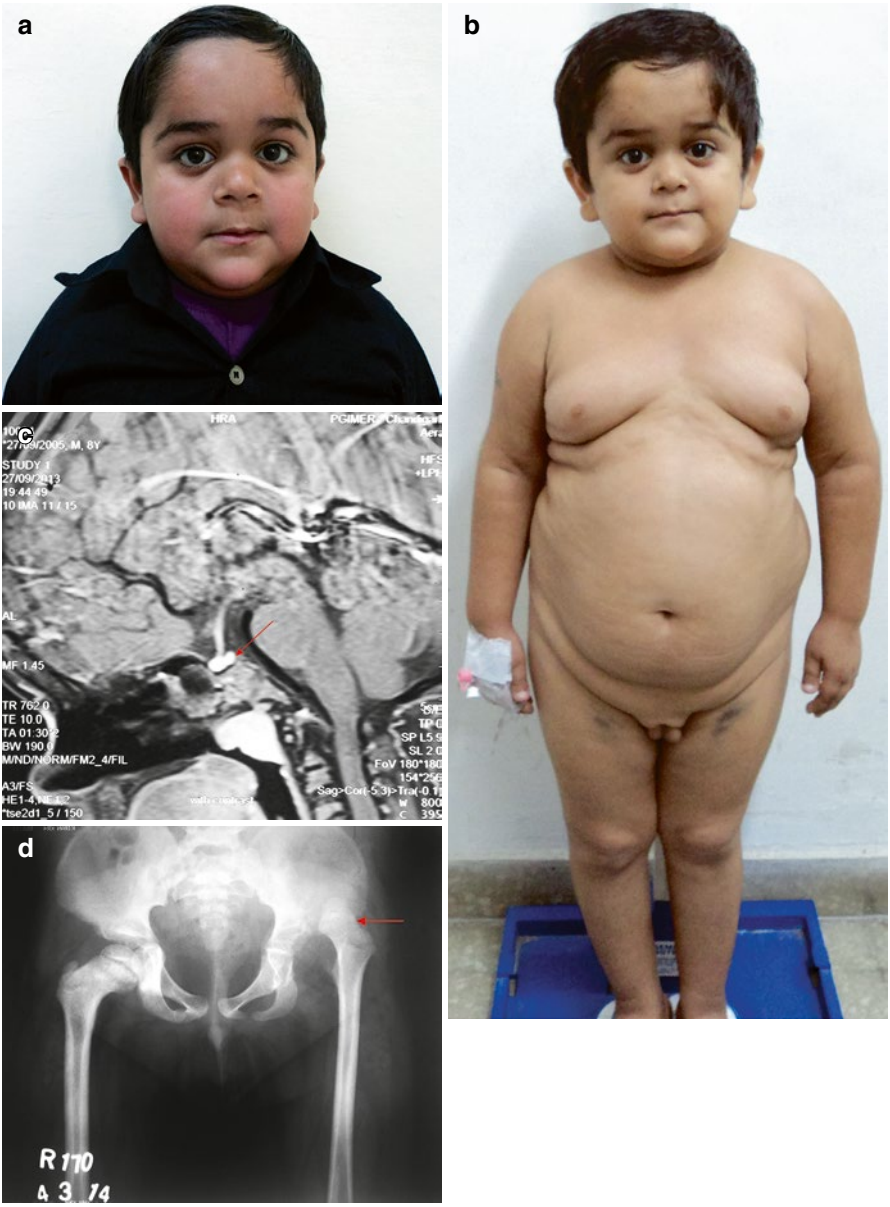


Fig. 1.1 A child with GH deficiency. Note (**a**) cherubic face, frontal bossing and midfacial hypoplasia (**b**) short stature, micropenis, and lipomastia. (**c**) CEMRI sella showing hypoplastic pituitary (*red arrow*). (**d**) X-ray pelvis demonstrating congenital hip dislocation (*red arrow*). (**e**, **f**) Improvement in facial features and height gain after 2 years of rhGH therapy. (**g**) Growth chart showing catch-up growth after initiation of rhGH therapy

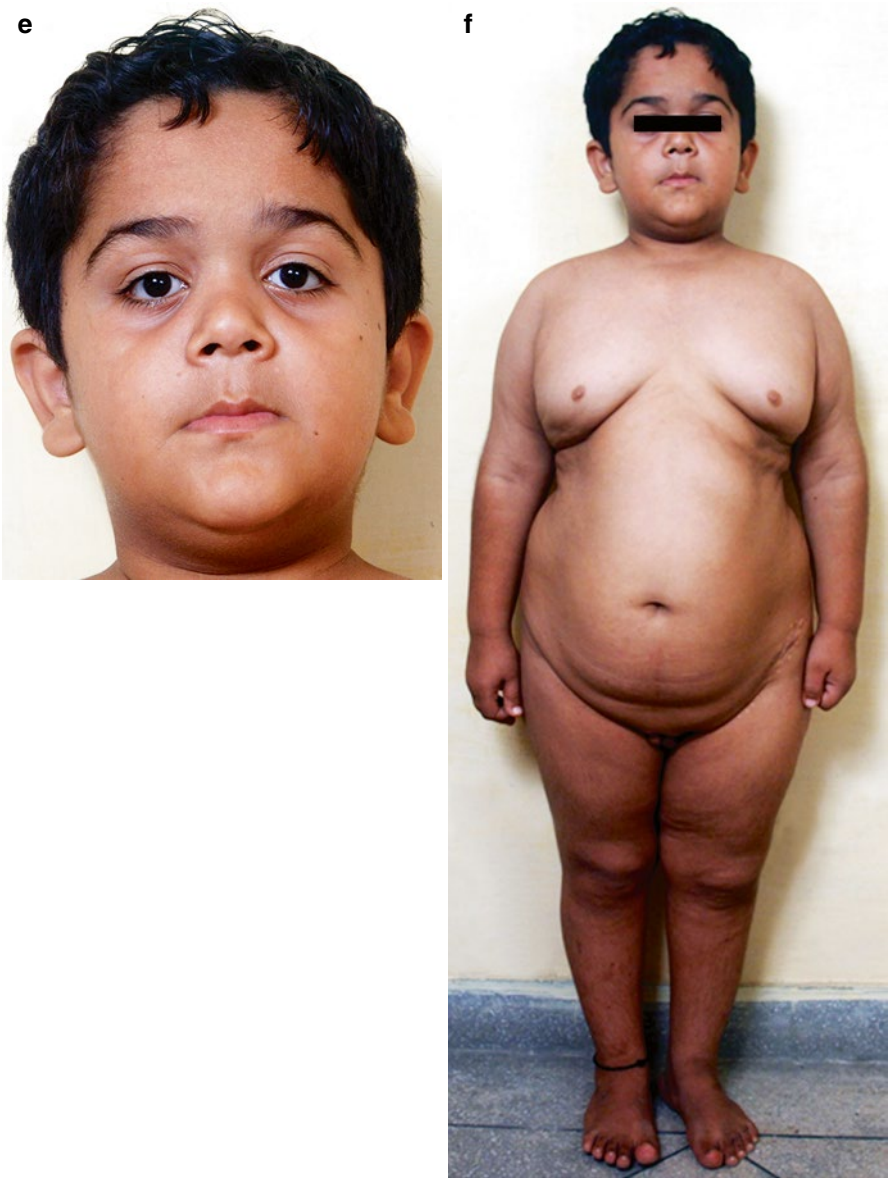


Fig. 1.1 (continued)

g

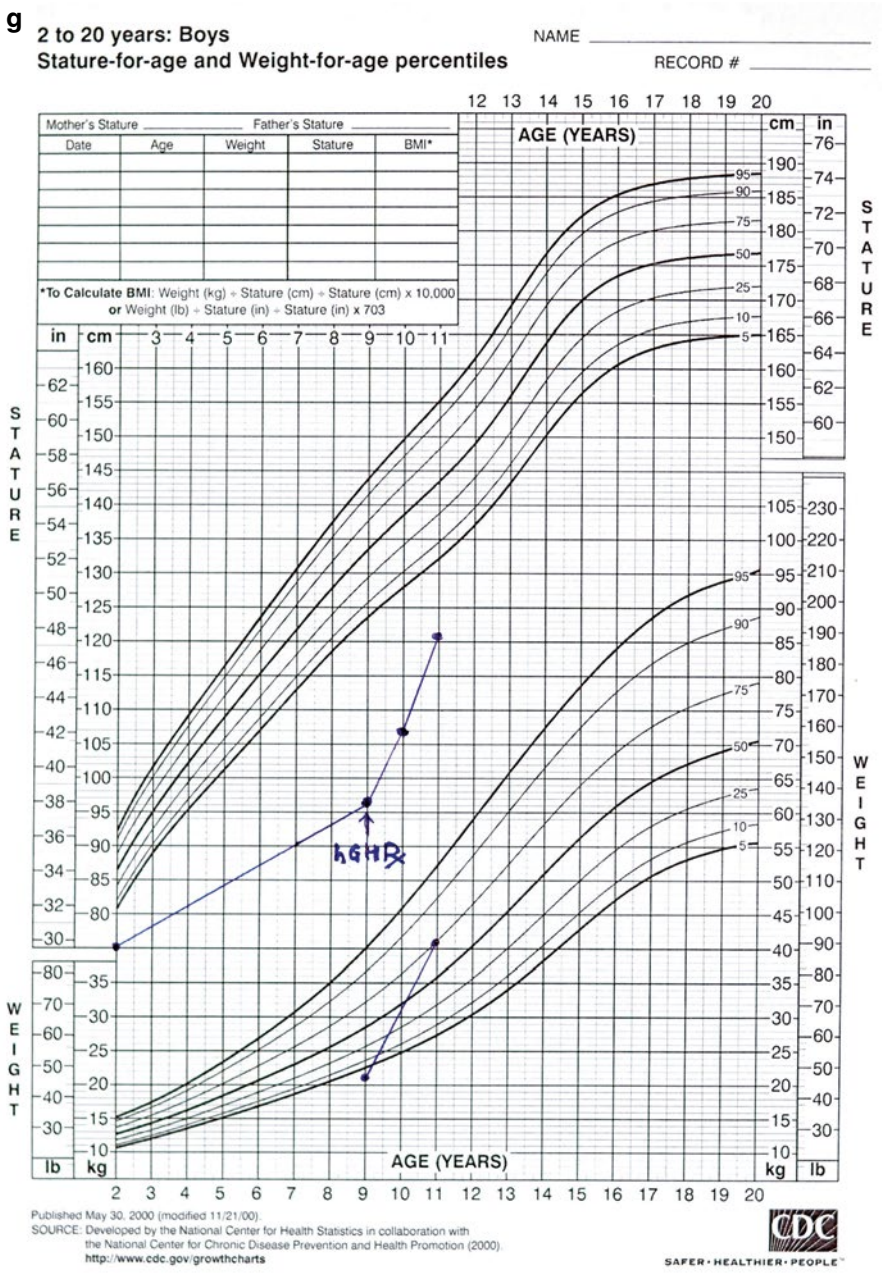


Fig. 1.1 (continued)

1.2 Stepwise Analysis

The index child was born of full-term normal vaginal delivery with birth weight of 3.3 Kg, thereby mitigating the possibility of intrauterine growth retardation as the cause of short stature. The birth length is usually normal in neonates with congenital growth hormone deficiency as intrauterine growth is GH independent and is predominantly dependent upon maternal nutritional status, uteroplacental blood flow, placental IGF1 and IGF2, and fetal insulin. Prolonged physiological jaundice and micropenis (stretched penile length <2.5 cm) are the clues to suspect congenital growth hormone deficiency in the index child. Prolonged physiological jaundice is a result of decreased glucuronyl transferase activity, as this enzyme requires initial activation by GH, thyroxine, and cortisol. Besides GH deficiency, micropenis may be due to intrauterine testosterone deficiency. Other manifestation of congenital GH deficiency is neonatal hypoglycemia, which was not present in our patient. Neonatal hypoglycemia is a result of decreased GH-mediated hepatic gluconeogenesis and glycogenolysis. Further, breech presentation has also been shown to be associated with congenital GH deficiency; however, the cause and effect association between breech presentation and GH deficiency remains conjectural. Optimal nutrition is the key factor in determining the growth during infancy, while GH is essential for growth throughout the childhood, and along with gonadal steroids it results in pubertal growth spurt. The growth faltering in the index patient was evident even at the age of 1 year. The child continued to have growth velocity of 3 cm/year which is subnormal for the prepubertal age (5–6 cm/year). Any child who has growth faltering or has height SDS of <−3 requires urgent evaluation. The index patient had growth faltering as well as height SDS of −7, therefore he required immediate evaluation. Systemic disorders as a cause of short stature was unlikely in our patient, as weight is more severely compromised than height in these disorders, as opposed to endocrine disorders where height is more severely compromised than weight, as was seen in our patient (height age 3 years, weight age 6 years). After exclusion of systemic disorders, common endocrine disorders associated with short stature which should be considered in our patient include growth hormone deficiency, Cushing's syndrome, juvenile primary hypothyroidism, and obesity–hypogonadism syndrome. The probability of Cushing's syndrome was less likely in our patient as his weight was <3rd percentile, and he did not have any stigma of protein catabolism, or moon facies, a characteristic feature of childhood Cushing's syndrome. Juvenile primary hypothyroidism was also less likely in our patient, as he did not have myxoedematous manifestations, and deep tendon reflexes were normal. Obesity–hypogonadism syndrome was also unlikely as these syndromes are usually associated with subnormal mental development, skeletal anomalies, retinitis pigmentosa, and neurodeficits. The possibility of CDGP was also unlikely as he had severe short stature and growth velocity 3 cm/year. Further, the body proportions can also help to define the cause of short stature as proportionate short stature is usually associated with growth hormone deficiency, Cushing's syndrome, and systemic disorders, whereas primary hypothyroidism, rickets–osteomalacia, and skeletal dysplasias are associated with disproportionate short stature. The expected upper segment to lower segment ratio (US/LS) at the age of 9 years is 1:1; however, in our patient it was 1.2 which may not be truly representative in this patient due to concurrent presence of congenital dislocation of hip. Delayed bone age is usually a feature of all endocrine and systemic disorders and

excludes the diagnosis of intrinsic short stature. The index patient had typical facies of growth hormone (GH) deficiency as he had frontal bossing, depressed nasal bridge, midfacial hypoplasia, and micrognathia. These features are attributed to GH deficiency as GH is required for maxillary and mandibular bone growth, and frontal bossing is due to apparent prominence of frontal bone in relation to midfacial hypoplasia. Further, not only GH but thyroxine is also required for the development of nasal bridge. In addition, micropenis and delayed bone age also support the diagnosis of GH deficiency. Further, the patient had congenital dislocation of the hip which has been described in children with growth hormone insensitivity syndrome, and possibly it may be incidental in our patient. Before proceeding to GH dynamic tests, optimal investigations were carried out for exclusion of chronic systemic disorders (chronic kidney disease, chronic liver disease, renal tubular acidosis, and celiac disease), hypothyroidism, and pseudohypoparathyroidism. Serum IGF1 should be estimated as a screening test for growth hormone deficiency; however IGF1 level within age-matched reference range does not exclude the GH deficiency, as the sensitivity of IGF1 to diagnose GH deficiency is only 70 %. The index patient had a low serum IGF1 level. There is plethora of provocative tests to assess the GH reserve; however, two tests are required to establish the diagnosis of GH deficiency as single test lacks the requisite specificity. The provocative tests should be carried out in the fasting state and euthyroidism should be achieved prior to performing the test. In addition, gonadal steroid should be replaced in those children who are in peripubertal age. Insulin-induced hypoglycemia is considered as the "gold standard" test, and the index patient underwent insulin-induced hypoglycemia and clonidine stimulation tests. Further, insulin-induced hypoglycemia test provides an opportunity of simultaneous assessment of hypothalamo–pituitary–adrenal axis. Peak GH response to both these stimuli was undetectable, and cortisol response to insulin-induced hypoglycemia was subnormal in the index patient, thereby substantiating the diagnosis of GH and ACTH deficiency. After confirmation of diagnosis of hypopituitarism, plain and CEMRI sellar–suprasellar region should be performed in these children. MRI findings may include the presence of mass lesion in sellar–suprasellar region (e.g., craniopharyngioma) and classic tetrad (small sella, hypoplastic pituitary, redundant stalk, and ectopic posterior pituitary bright spot) suggestive of pituitary transcription factor defects (e.g., Pit-1 and PROP-1) or may be normal (e.g., idiopathic growth hormone deficiency). The index patient had small sella and hypoplastic pituitary. With this profile the diagnosis of multiple pituitary hormone deficiency was considered as he had GH, ACTH, and prolactin deficiency possibly due to pituitary transcription factor defect. He was initiated with rhGH at a dose of 0.3 mg/Kg/week and hydrocortisone at a dose of 10 mg/m^2. He had height gain of 11 cm in first year and 14 cm in second year of rhGH therapy. The expected gain in the first year after initiating rhGH therapy is approximately 10–12 cm followed by 8–10 cm in the second year and then progressively declines to 5 cm/year. The gradual decline in growth velocity has been attributed to "chondrocyte senescence." The greater height gain during second year as compared to first year of rhGH therapy in our patient can be attributed to corrective surgery for congenital dislocation of hip and replacement with L-thyroxine after unmasking of hypothyroidism due to concurrent TSH deficiency and possibly due to sustained growth response as he had severe GH deficiency. Development of hypothyroidism during rhGH therapy in our patient was either as a result of inhibition of TSH by increased somatostatin tone after rhGH therapy or as

evolution of de novo TSH deficiency. Weight-based dosage is recommended for the initiation of rhGH therapy and monitoring is performed with anthropometric measurement. IGF1-targeted GH therapy is not recommended, but serum IGF1 should be monitored annually to avoid IGF1 levels above the reference range which may be associated with adverse events. The side effects associated with rhGH therapy include slipped capital femoral epiphysis, benign intracranial hypertension, gynecomastia, kyphoscoliosis, and glucose intolerance. The child should be monitored at three to six monthly intervals for auxology, pubertal development, and adverse events. In addition, serum T_4 and cortisol should also be monitored initially at 3 months of rhGH therapy and thereafter annually. Manifestations of hypocortisolism may appear on rhGH therapy either as a result of increased catabolism of cortisol due to inhibition of 11β-hydroxysteroid dehydrogenase type 1 or evolution of underlying ACTH deficiency as a part of multiple pituitary hormone deficiency. Early diagnosis of GH deficiency and timely initiation of rhGH therapy may be rewarding to achieve the adult target height in short children. Regular follow-up and periodic monitoring of evolution of other hormone deficiency are essential for optimal outcome.

1.3 Clinical Rounds

1. *How to define short stature*?

   A child with height two standard deviation below the mean (−2SD or 2.3rd percentile) as compared to children of the same age, gender, and race is considered to have short stature. In a normally distributed population (Gaussian distribution), height of 95% of individuals falls within 2SD from the population mean. The probability of detecting a child with growth disorder is higher in individuals who are 2SD above or below the mean. Therefore, a height 2SD below the mean is used to define short stature.

2. *What is the normal growth pattern during childhood*?

   The normal growth is reflected by the progressive increase in auxological parameters like height, weight, and head circumference in reference to the established standards for that particular age, gender, and race. The mean length of a healthy newborn is 50 cm and grows at height velocity of 25 cm in the first year, 12 cm in the second year, 8 cm in the third year, and 5 cm per year thereafter till the onset of puberty. Therefore, a child doubles his birth length by 4 years of age. In addition, height at the age of 2 years is approximately half of the individual's final adult height. The pubertal growth spurt is approximately 28 cm in boys and 25 cm in girls, which corresponds to a height velocity of 9.5 cm per year in boys and 8.3 cm per year in girls. A newborn looses up to 10% of birth weight during the first week of life and thereafter starts gaining weight. The weight of a child doubles by 4 months of age, triples by 1 year, and quadruples by 2 years of age. The head circumference is 32–35 cm at birth, 43–46 cm by the first year, 49 cm by the second year, and reaches adult value (56 cm for males, 54 cm for females) by 5–6 years of age. Height velocity of a healthy growing child is given in the table below.

Age	Height velocity (per year)
Birth	–
0–1 year	25 cm
1–2 year	12.5 cm
2–3 year	8 cm
3 years – puberty	5 cm
Puberty	
Boys	9.5 cm
Girls	8.3 cm

3. *What are the determinants of fetal growth*?

The determinants of fetal growth include maternal nutritional status, placental sufficiency, placental insulin-like growth factor 2 (IGF2) and IGF1, and fetal insulin. In addition, various growth factors like epidermal growth factor, fibroblast growth factor, nerve growth factor, and parathyroid hormone-related peptide (PTHrP) also play an important role in fetal growth. Although, GH has important role in postnatal growth, it has minimum effect on intrauterine growth as evidenced by GH receptor knockout mice which has normal size at birth.

4. *What is the role of insulin-like growth factors in fetal growth and development*?

Placental insulin-like growth factors (IGF1 and IGF2) play an important role in fetal growth and development. It has been shown in mice that deletion of either IGF1 or IGF2 gene results in low birth weight (60 % of normal), whereas deletion of type 1 IGF receptor (IGF1R) results in greater reduction in birth weight (45 % of normal). This is because both IGF1 and IGF2 act through IGF1R to promote fetal growth. However, type 2 IGF receptor (IGF2R) is important in the regulation of IGF2 action by increasing its turnover. The table given below illustrates the effects of insulin and IGF1/IGF2 on fetal growth and development.

Animal model	Birth weight
IGF1 gene knockout mice	60 % of normal
IGF2 gene knockout mice	60 % of normal
Combined IGF1 and IGF2 gene knockout mice	30 % of normal
IGF1 R knockout mice	45 % of normal
Combined IGF1 gene and IGF1R knockout mice	45 % of normal
Combined IGF2 gene and IGF1R knockout mice	30 % of normal
IGF2 R knockout mice	130 % of normal
Insulin receptor knockout mice	Normal
Insulin gene knockout mice	78 % of normal

5. *What is the role of parathyroid hormone-related peptide in fetal growth and development*?

Parathyroid hormone-related peptide (PTHrP) plays an important role in fetal growth and development by facilitating transplacental transport of calcium and

promoting uteroplacental blood flow. In addition, it also regulates the growth and differentiation of chondrocytes during fetal life. The role of PTHrP in fetal growth is evidenced by short stature and skeletal dysplasia in patients harboring PTHrP receptor mutations; activating mutations cause Blomstrand dysplasia and inactivating mutations cause Jansen chondro-osteodystrophy.

6. *Is growth of a child exclusively GH-dependent*?

   A child with congenital growth hormone deficiency (GHD) has near-normal birth length. However, there is a rapid decline in height velocity by the age of 2 years in these children; thereafter, they continue to grow at a reduced height velocity. If left untreated, the child can attain a final adult height which is approximately 70 % of his/her genetic potential, with a height deficit of 38 cm in males and 33 cm in females. This suggests that growth is not exclusively a GH-dependent phenomenon and other hormones also play a role.

7. *What are the determinants of postnatal growth*?

   Postnatal growth is determined by nutritional factors, hormones, and genetic potential of an individual. During infancy, growth is predominantly influenced by nutritional status of the child. During the prepubertal period, hormones like GH–IGF1, thyroxine, and insulin play an important role, while pubertal growth spurt is caused by progressive increase in gonadal steroids and the consequent GH–IGF1 surge. However, the final height of an individual is determined by his/her genetic potential. This is possibly attributed to predetermined chondrocyte potential for skeletal growth, IGF1 sensitivity, rate of ossification maturation, and ethnicity of an individual.

8. *What are the hormones required for postnatal growth*?

   Growth hormone and IGF1 are the prime mediators of postnatal linear growth. GH-mediated IGF1 generation is facilitated by nutritional status, insulin, thyroxine, gonadal steroids, and, possibly, vitamin D. In an individual, limb growth is predominantly dependent on GH–IGF1, while truncal growth on gonadal steroids. Thyroxine, insulin, and testosterone not only facilitate GH-mediated IGF1 generation but also promote GH-independent IGF1 generation. Further, insulin acts directly on IGF1 R, albeit at a much lower affinity (100-fold less) than IGF1. Estrogen in low concentration promotes GH-mediated IGF1 generation but, in high concentration, inhibits IGF1 generation. Testosterone stimulates GH-mediated IGF1 generation by its direct effect and by aromatization to estrogen. In addition, it also promotes GH-independent IGF1 generation by its direct effect on hepatocytes.

9. *What is the structure of epiphyseal growth plate*?

   The growth plate, also known as physis, is present between the epiphysis and metaphysis at the ends of long bones. It comprises of five zones: resting zone, proliferative zone, hypertrophic zone, calcification zone, and ossification zone,

from epiphysis to metaphysis. The process of linear growth initiates at the epiphyseal end of growth plate and new bone is laid down at the metaphysis (Fig. 1.2a, b).

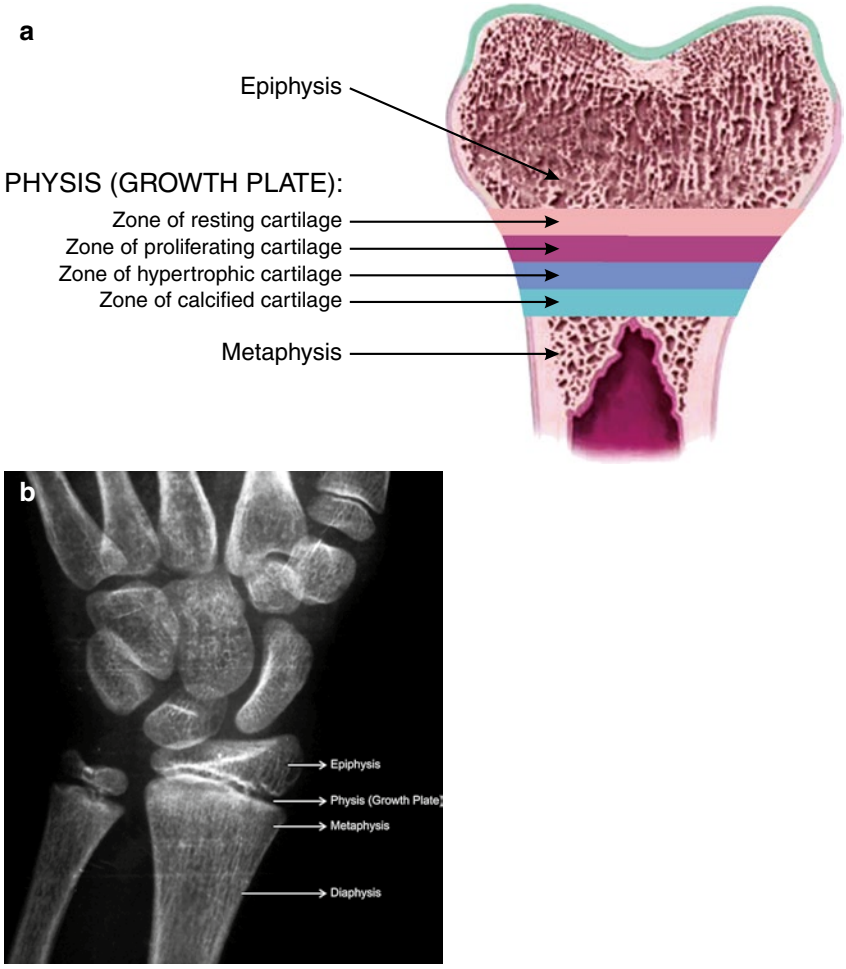


Fig. 1.2 (**a**) Showing different zones of growth plate. (**b**) X-ray wrist AP view showing physis (growth plate) as a radiolucent area between epiphysis and metaphysis

10. *How does linear growth occur in a child*?

Linear growth is a result of a well-regulated and coordinated process called "chondro-osteogenesis," which includes chondrocyte proliferation, differentiation/hypertrophy, apoptosis, and endochondral ossification. Longitudinal bone growth occurs at the epiphyseal growth plate located at the ends of long bones. In the resting zone, there is a reserve of chondrocytes, which proliferate under the influence of GH and IGF1. These proliferating chondrocytes enlarge to hypertrophic chondrocytes in the presence of IGF1, thyroid hormones, and gonadal steroids. The paracrine factors that help in chondrocyte proliferation and hypertrophy include PTHrP, IHH, BMPs, FGFs, RUNX2, and SOX9.

These terminally differentiated cells eventually undergo apoptosis. Later, the growth plate is invaded by blood vessels and bone cell precursors from metaphysis, resulting in remodeling of cartilage into bone, a process termed as endochondral ossification. The various endocrine and paracrine factors that regulate "chondro-osteogenesis" are depicted in the figure given below (Fig. 1.3).

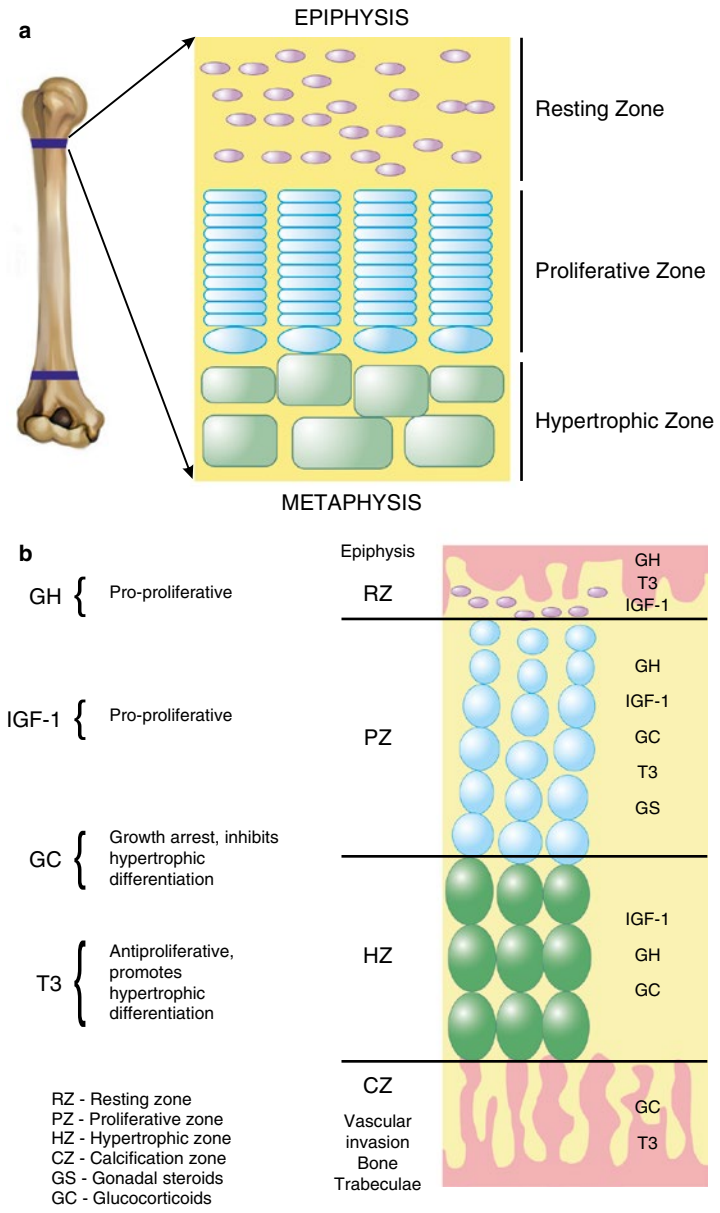


Fig. 1.3 (**a**) Different zones of growth plate. (**b**) Site of action of various endocrine and paracrine factors on growth plate

11. *How does circumferential bone growth occur in a child*?

The linear bone growth occurs at epiphyseal growth plate (at the end of long bones), while circumferential bone growth (appositional bone growth) occurs beneath the periosteum at diaphysis. The appositional bone growth is the result of intramembranous ossification, where osteoblast forms the new bone just beneath the periosteum. Estrogen inhibits, while androgen and GH stimulate appositional bone growth at diaphysis. Periosteal new bone formation is accompanied with endosteal bone resorption as the new bone formation exceeds bone resorption at periosteum and vice versa at endosteum, thereby resulting in increased circumferential bone growth (Fig. 1.4).

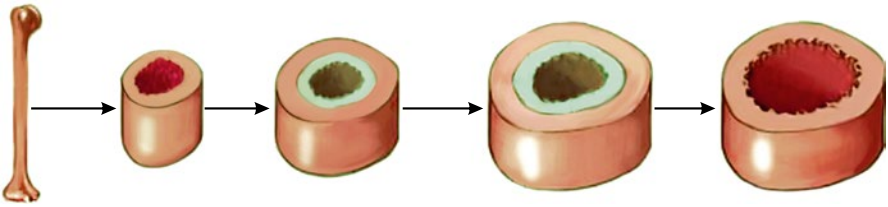


Fig. 1.4 Circumferential growth of a long bone

12. *How does growth hormone promote linear growth*?

Growth hormone promotes linear growth through systemic (liver) and locally derived (growth plate) IGF1. In addition, GH per se has a direct effect on growth plate, independent of IGF1. GH–IGF1 is responsible for the differentiation of pre-chondrocytes to chondrocytes, followed by the proliferation and maturation of chondrocytes in the epiphyseal growth plate. Further, GH–IGF1 also promotes bone collagen synthesis.

13. *What are the hormones responsible for GH-independent IGF1 generation*?

IGF1 generation is predominantly a GH-dependent phenomenon which is facilitated by thyroxine, insulin, and gonadal steroids. However, thyroxine, insulin, and gonadal steroids also promote GH-independent IGF1 generation. This is evidenced by the fact that children with GH deficiency/GH receptor mutation continues to grow, albeit at a lower height velocity, with measurable levels of serum IGF1, which suggest GH-independent IGF1 generation. In addition, these hormones also have a direct effect on epiphyseal growth plate and promote chondrocyte proliferation.

14. *Why are the boys taller than girls*?

Boys are taller than girls because of physiological delay in the initiation of puberty by a period of 2 years (thereby yielding two additional years of cumulative linear growth), more intense pubertal growth spurt, and presence of growth-promoting genes on Y(Yq) chromosome. The average difference in height between adult men and women is 13 cm. This difference is due to growth accumulated during two additional prepubertal years (10 cm) and the greater gain in

height during pubertal growth spurt (3 cm) in boys. This knowledge is important and is used in the calculation of midparental height of an individual.

15. *What are the causes of growth without growth hormone*?

Linear growth is a GH–IGF1-dependent phenomenon; however, there are disorders where growth is GH-independent. Childhood obesity is one of the paradoxical situations where there is an accelerated linear growth with low levels of GH. The other causes of growth without GH include craniopharyngioma (hypothalamic dysfunction-induced adiposity), childhood hyperthyroidism, Beckwith–Wiedemann syndrome (IGF2-mediated growth), and Soto's syndrome (NSD1 mutation).

16. *Why do obese children have higher growth velocity despite low GH*?

Obesity in childhood and adolescence is associated with increased height velocity with low basal as well as stimulated GH levels, normal total IGF1, and increased "free" IGF1. Obesity-induced hyperinsulinemia promotes GH-independent IGF1 generation, increases free IGF1 level by reducing IGFBP1, and directly stimulates IGF1 receptor, thereby resulting in accelerated linear growth. Elevated levels of "free" IGF1 increase somatostatin tone, resulting in decreased GH secretion. In addition, there is an increase in leptin levels in obese children, which also acts as skeletal growth factor. Further, increased aromatization of androgens to estrogens as a result of excess adiposity also contributes to the linear growth. However, the final adult height in obese children does not differ from nonobese children, as a result of early puberty and excess aromatization of androgens leading to premature epiphyseal closure (Fig. 1.5).

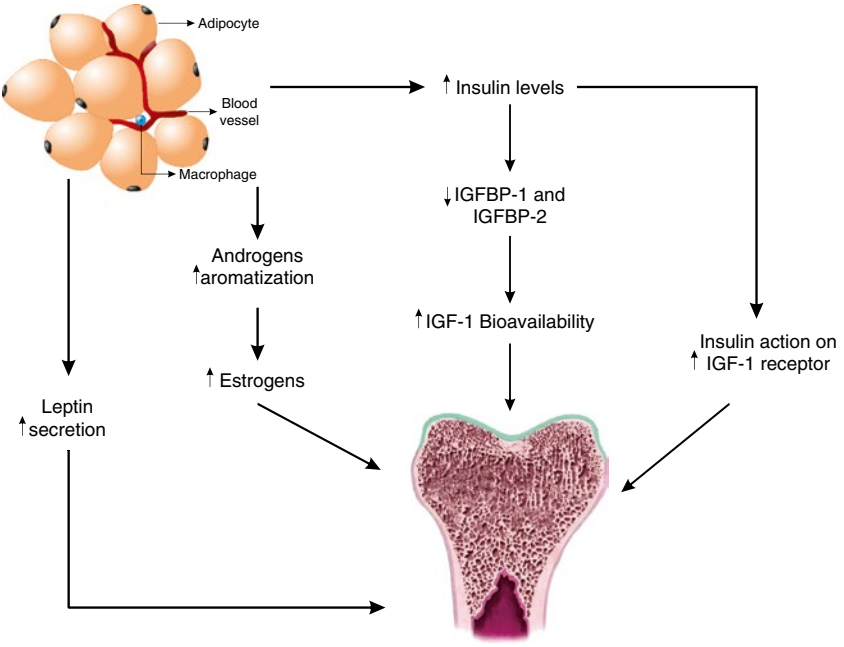


Fig. 1.5 Mechanisms of obesity-related accelerated growth velocity

17. *Why is total IGF1 level normal despite low GH levels in obesity*?

    Obesity is associated with normal IGF1 despite low GH level. This is due to GH-independent, insulin-mediated IGF1 generation and enhanced GH sensitivity because of upregulation of GH receptors, as evidenced by increase in GH-binding proteins (GHBP).

18. *A 6-year-old obese child presented with short stature. Is it of concern*?

    Childhood obesity is associated with normal/accelerated height velocity. Therefore, presence of short stature in an obese child is almost always pathological and should be evaluated further. The common causes of short stature with obesity include Cushing's syndrome, hypothyroidism, isolated growth hormone deficiency, pseudohypoparathyroidism, and Prader–Willi syndrome.

19. *What are the hormones responsible for the development of facial features*?

    Hormones responsible for the development of facial features are thyroxine, GH–IGF1, and gonadal steroids. Thyroxine is responsible for facial bone growth and maturation during prenatal and infantile period. Infants with congenital hypothyroidism therefore have characteristic facial features including immature facies, flat nasal bridge, and pseudohypertelorism. GH–IGF1 is mainly responsible for facial features during prepubertal period. Therefore, patients with congenital growth hormone deficiency manifest with frontal bossing, midfacial hypoplasia, and micrognathia. During peripubertal period, gonadal steroids play an important role in facial maturation and lead to sexual dimorphism in the facial characteristics (Fig. 1.6).

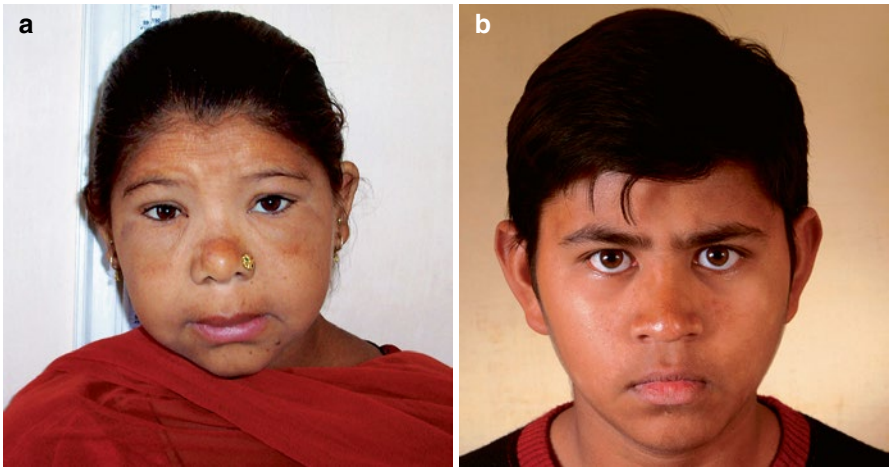


Fig. 1.6 (**a**) Characteristic facial features in a girl with congenital hypothyroidism. (**b**) Immature facies in an adolescent with hypogonadism