Clinical Rounds in Endocrinology

Volume I
Adult Endocrinology

Anil Bhansali
Yashpal Gogate

Springer

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Dedicated
to
My beloved mother late Smt Munna Kumari Bhansali,
the inspiring force in my life,
My father Shri M L 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

Clinical endocrinology is a wide-ranging, complex, and fast-moving medical discipline. The current volume of "Clinical Rounds in Endocrinology" captures the intricate nature of endocrinology by introducing case vignettes and discussing the steps how the diagnostic workup, differential diagnosis, and treatment modalities could lead to the best care of the patient. The succinct description of the case presentation is followed by short questions, each discussed in a paragraph summarizing the main points relevant for the management. This format is different from the usual handbook or textbook format and provides a unique insight and quick reference, not available elsewhere even in today's era of overwhelming information available on the Internet. This aspect makes this book unique and first of its kind in modern endocrinology.

Over the past years, much progress has been made in this field, with the introduction of better imaging and biochemical diagnostic tools and widening pharmacological treatments in addition to surgery and radiotherapy. This volume will help the practicing clinician to keep up to date with the novel diseases, diagnostic modalities, and management of these sometimes very rare diseases. The book comprises of 20 informative chapters. Five chapters are dedicated to pituitary-related diseases such as acromegaly and Cushing's syndrome, and there are four chapters discussing thyroid disorders including an informative section on pregnancy-related thyroid disease, three chapters on adrenal-related subjects, and three on bone and electrolyte household. The last five chapters cover type 1 and type 2 diabetes, diabetes complications, and management of pregnancy with diabetes. Fast advances in diagnostic modalities, such as PET scanning combined with novel isotope scannings or in genetics of endocrine diseases, such as the flurry of novel genes for pheochromocytoma and paraganglioma syndromes, are also expertly discussed in the relevant chapters.

The book covers most of the clinical endocrine field, they provide useful reference and practical tools for managing conditions that are relevant for clinicians involved in the care for patients with endocrine diseases, and I expect that it will be of interest not only for endocrinologists or under- and postgraduate students of endocrinology but also for internists, pediatricians, surgeons, radiologists, clinical geneticists, and radiotherapists active in this field.

The book provides excellent and often unique illustrative photographs and tables to facilitate the full understanding of the topic. The chapters are written by Prof Anil Bhansali, Head of Department of Endocrinology at the Postgraduate Medical

Institute (PGIMER), Chandigarh, India, and by Dr. Yashpal Gogate and their team members including Dr. Girish P. and Dr. Anuradha Aggarwal. This book shows the remarkable breadth and depth of their clinical knowledge, and this handbook will turn soon into a classic reference volume for students, trainee endocrinologists, and practicing endocrinologists worldwide.

London, UK Marta Korbonits, MD, PhD

Preface

Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh is one of the premier medical and research institutes in India. This tertiary healthcare center, right from its days of inception, has always been at the forefront in the field of medical science. Endocrinology, as a super speciality department, was established way back in 1964 for the first time in India at PGIMER, Chandigarh.

This department has a long-standing tradition of academic rounds, with detailed discussions pertaining to every aspect of patient care, right from symptom analysis, demonstration and interpretation of signs, formulation of differential diagnosis, judicious use, and analysis of investigations and management strategies. This legacy of clinical rounds was inherited from my great teacher, Professor R.J. Dash, who had enormous knowledge of the subject with a great ability of critical analysis. Several thought-provoking questions are spontaneously generated during these interactive sessions with inputs and suggestions by residents and views and counterviews by faculty members. This continuous process of exchange of knowledge helps in providing the best possible medical care to our patients. Therefore, we had a thought to compile this information in the text that will facilitate dissemination of the knowledge to physicians and endocrinologists. Further, I had a long-cherished dream to write a book in endocrinology with precise information, comprehensive knowledge, and critical analysis of the facts.

One fine day, I expressed my desire to write a book to my student Yashpal, who not only appreciated this thought but also helped me in materializing the dream. It was decided to write a book in a "question and answer" format as this pattern not only simulates clinical rounds, but will also help the healthcare professionals in dealing with challenges in day-to-day practice. This book includes 20 chapters covering disorders of the pituitary, adrenal, thyroid, and parathyroid glands and diabetes and metabolic bone disease. 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.

The framework of the book was created by me and helped by Dr. Yashpal over a period of 7 months. Later, my students, Dr. Girish Parthan and Dr. Anuradha Aggarwal, worked untiringly with me for the next 1 year in reviewing the literature,

adding clinical images, tables, and illustrations and finally editing the text to final the book in its final shape. The whole process in itself was a great learning experience.

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

Chandigarh, India — Anil Bhansali
Nasik, India — Yashpal Gogate

Acknowledgments

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 the book, though a few names with a lion's share in the completion of the book are mentioned.

I, Dr. Anil Bhansali, would like to thank my colleagues Dr. Sanjay Kumar Bhadada, Dr. Pinaki Dutta, Dr. Rama Walia, Dr. Ashu Rastogi, and Dr. Naresh Sachdeva for their valuable suggestions and continuous support.

We sincerely appreciate the effort of Dr. Girish and Dr. Anuradha, for their immense contribution to this book. They have indeed inculcated "soul" to the book.

We thank all residents including Dr. Dheeraj Solanki, Dr. Soham Mukherjee, Dr. Mandeep Singla, Dr. Abhishek Hajela, Dr. Suja P Sukumar, Dr. Kushdev Jariyal, Dr. Vikram Shekhawat, and Dr. Rajneesh Mittal for their help and encouragement.

We also thank Prof. B.R. Mittal and Dr. Anish Bhattacharya from the Department of Nuclear Medicine, Prof. Paramjit Singh and Dr. Chirag Ahuja from the Department of Radio Diagnosis, and Prof. Uma Nahar from the Department of Histopathology 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 really admire my friends Justice Hari Pal Verma and Harish Singla for their continuous encouragement and support. I, Dr. Yashpal Gogate, sincerely thank my wife Dr. Ketki and my parents Dr. Vinita and Dr. Vikas Gogate.

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 for acquisition of the clinical images. We also thank Mrs. Rama Puri and Mr. Mahabir Singh for their uninterrupted assistance throughout the period of writing this book.

We are also grateful to all our patients who have helped us in learning clinical endocrinology.

We are also thankful to our publisher Springer and their team members Dr. Naren Aggarwal, Teena Bedi and Mr. Durai Gangapattla.

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.

Chandigarh, India — Anil Bhansali
Nasik, India — Yashpal Gogate

Contents

Authors

Anil Bhansali pursued his DM in endocrinology in 1989 from the Postgraduate Institute of Medical Research (PGIMER), Chandigarh, and is currently the Professor and Head of the department at the same institute. His areas of interest include adrenals, gonads, and type 2 diabetes mellitus. He is actively involved in research and clinical activities and has more than about 300 publications in various national and international journals. He also is the author of many chapters in various textbooks. He is the recipient of Prof. M.N. Sen ICMR Award, Prof. M. Vishwanathan Award, and Prof. Shurvir Singh Award, among others. He is also the Consulting Editor to the Indian Journal of Endocrinology and Metabolism and the past president of the Endocrine Society of India. Presently, he is actively involved in stem cell research and in establishing a state-of-the-art diabetic foot laboratory and facilities for clamp studies.

Yashpal Gogate completed his DM in Endocrinology from the Postgraduate Institute of Medical Research (PGIMER), Chandigarh. Currently, he is working as an Assistant Professor at Dr Vasantrao Pawar Medical College, Nasik, and is also a Consultant Endocrinologist at Harmony Health Hub, Nasik. He has a passion in teaching graduate and postgraduate medical students. He has been the recipient of the Jal Mehta Award in Community Medicine. His areas of interest include diabetes, thyroid disorders, and polycystic ovarian disease.

Acromegaly: Clinical Perspectives

1

1.1 Case Vignette

A 27-year-old male, presented with an episode of generalized tonic clonic seizures, altered sensorium, and rapid breathing. He was diagnosed to have diabetes mellitus about 6 months back and despite being on insulin had poor glycemic control. He had no family history of diabetes. There was history of acral enlargement for the past 8 years. He complained of intermittent episodes of headache, but did not have any visual disturbances. On examination, he was dehydrated, had a blood pressure of 100/60 mm of Hg, and was tachypneic. He had florid manifestations of acromegaly and had no goiter. There was diffuse hyperpigmentation. Although he was dehydrated, he had hyperhidrosis and seborrhea. At presentation, blood glucose was 550 mg/dl, HbA1c 17%, serum β-hydroxybutyrate 6.1 mmol/l, and arterial blood gas analysis revealed high anion gap metabolic acidosis. He was treated with intravenous saline and insulin infusion, with an insulin requirement around 200 units per day. Diabetic ketoacidosis gradually resolved, and he was switched to basal-bolus regimen with an insulin requirement of 100 units per day. His height was 176 cm and weight 80 kg with a BMI of 25.8 kg/m^2. Serum electrolytes, calcium profile, and renal and liver function tests were normal. Hormonal workup showed T_4 3.5 μg/dl (4.8–12.7), TSH 1.2 μIU/ml (0.27–4.2), 0800 h cortisol 592.6 nmol/L (171–536), ACTH 35 pg/ml (5–60), 0800 h serum cortisol after 1 mg dexamethasone 40 nmol/L (<50), prolactin 17.9 ng/ml (4.0–15), and testosterone 1.3 nmol/L (9.9–27.8). Serum insulin like growth factor 1 (IGF1) was 769.6 ng/ml (116–358), and growth hormone (GH) following glucose tolerance test was 120 ng/ml (<1 ng/ml). MR imaging showed a sellar–suprasellar mass of 4.8 × 3.2 × 3.5 cm abutting the optic chiasm, and his visual field examination confirmed bitemporal hemianopia. He was diagnosed as acromegaly due to macrosomatotropinoma, with secondary diabetes, diabetic ketoacidosis, secondary hypothyroidism, and hypogonadism. Genetic analysis for MEN1 and familial isolated pituitary adenoma (FIPA) was negative. He was started on levothyroxine and testosterone replacement therapy. He underwent transsphenoidal pituitary surgery uneventfully. He did not have

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CSF rhinorrhea, but had polyuria which resolved after 3 days. Postoperative day 2 serum GH was 4 ng/ml and cortisol was 450 nmol/L. His insulin requirement reduced substantially to 50 units per day. At 3 months he was reevaluated and had a serum IGF1 450 ng/ml and GH 3 ng/ml following glucose load suggestive of residual functioning somatotropinoma. Serum T_4 was 7.4 μg/dl and testosterone 7.0 nmol/L on levothyroxine and testosterone replacement and 0800 h cortisol 400 nmol/L. MR imaging showed a residual adenoma of size $1.2 \times 1.1 \times 0.8$ cm, and he is planned for ϒ-knife therapy.

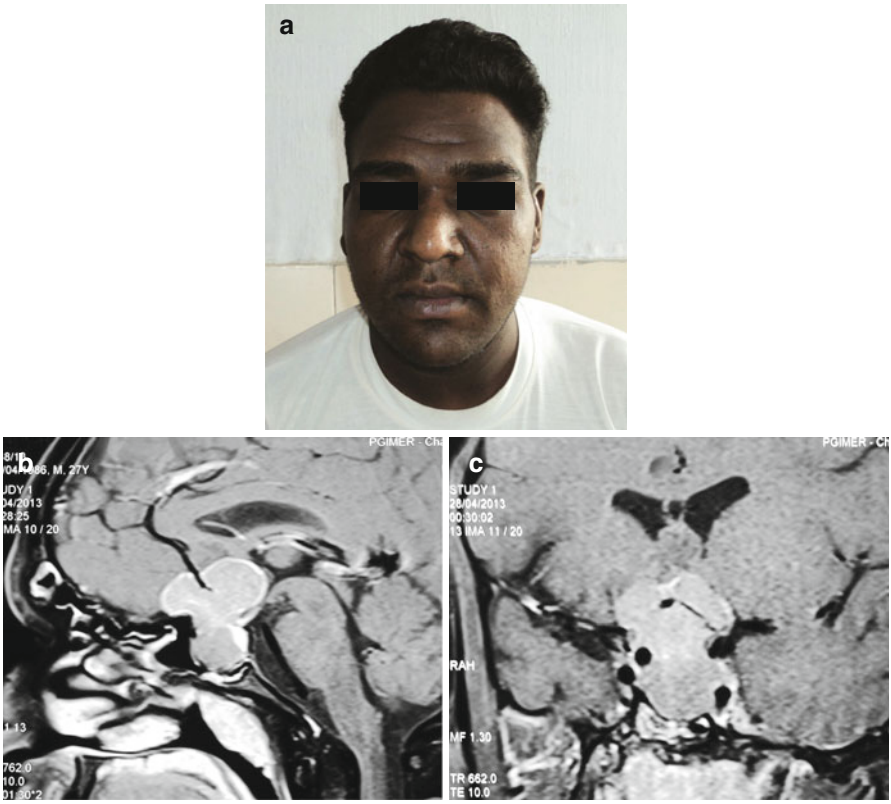

Fig. 1.1 (**a**) Patient with typical features of acromegaly along with hyperpigmentation. (**b**) Contrast-enhanced T1 MR sagittal image showing lobulated sellar–suprasellar mass abutting optic chiasm. (**c**) T1W CEMR coronal image showing pituitary macroadenoma with partial encasement of bilateral cavernous ICA segments without significant luminal compromise

1.2 Stepwise Analysis

This patient had history of acral enlargement for the past 8 years, suggestive of insidious onset of disease which is a usual feature of acromegaly. He had active acromegaly as suggested by the progressive worsening of headache, new-onset visual field defects, hyperhidrosis, seborrhea, and uncontrolled blood glucose. Dysglycemia in acromegaly occurs in 50% of patients, and 15–20% have overt diabetes. However, presentation as diabetic ketoacidosis is uncommon in patients with acromegaly and only a handful cases have been reported in the literature. Diagnosis of secondary diabetes should have been considered initially in this patient in view of young age at onset, lack of family history of diabetes, and severe and resistant hyperglycemia. It is not surprising to have such tremendous requirement of insulin in secondary diabetes associated with acromegaly. Seizure in the index patient may be due to cerebral dehydration as a result of diabetic ketoacidosis. In the presence of hyperglycemia, the estimation of serum GH and IGF1 for the diagnosis of acromegaly is debatable, as chronic hyperglycemia per se is associated with high GH and low IGF1 levels. Ideally, serum IGF1 and GH post-glucose load should be measured after optimal blood glucose control in patients of acromegaly with diabetes. However, high IGF1 (age and gender matched) in the presence of chronic hyperglycemia favors a diagnosis of active acromegaly. Diffuse hyperpigmentation in a patient with acromegaly can occur due to the direct effect of GH on melanocytes, GH, and ACTH co-secreting tumor and rarely diffuse acanthosis nigricans because of severe insulin resistance. Diffuse hyperpigmentation in the index case was due to the direct effect of GH on melanocytes. Majority of patients with acromegaly have macrosomatotropinoma as was seen in this case. In view of GH excess since adolescence, he was evaluated for familial causes of somatotropinoma like MEN1 and FIPA, which were negative. Polyuria after transsphenoidal surgery in patients with acromegaly may be due to central diabetes insipidus or passage of glycosaminoglycans in urine after reduction in circulating GH levels. Serum and urine osmolality was normal, thereby the diagnosis of diabetes insipidus was excluded in this patient. Postoperative day 1–7 fasting serum GH level <2 ng/ml predicts the cure. However in the index patient, postoperative fasting serum GH was 4 ng/ml suggestive of residual disease. Serum IGF1 should not be used for monitoring in the immediate postoperative period as it takes long time to normalize after curative adenomectomy. The treatment options available for residual disease in acromegaly are somatostatin analogues, cabergoline, pegvisomant and ϒ-knife therapy. This patient was offered ϒ-knife therapy for the treatment of his residual disease, and cabergoline 1 mg per day was administered during interim period.

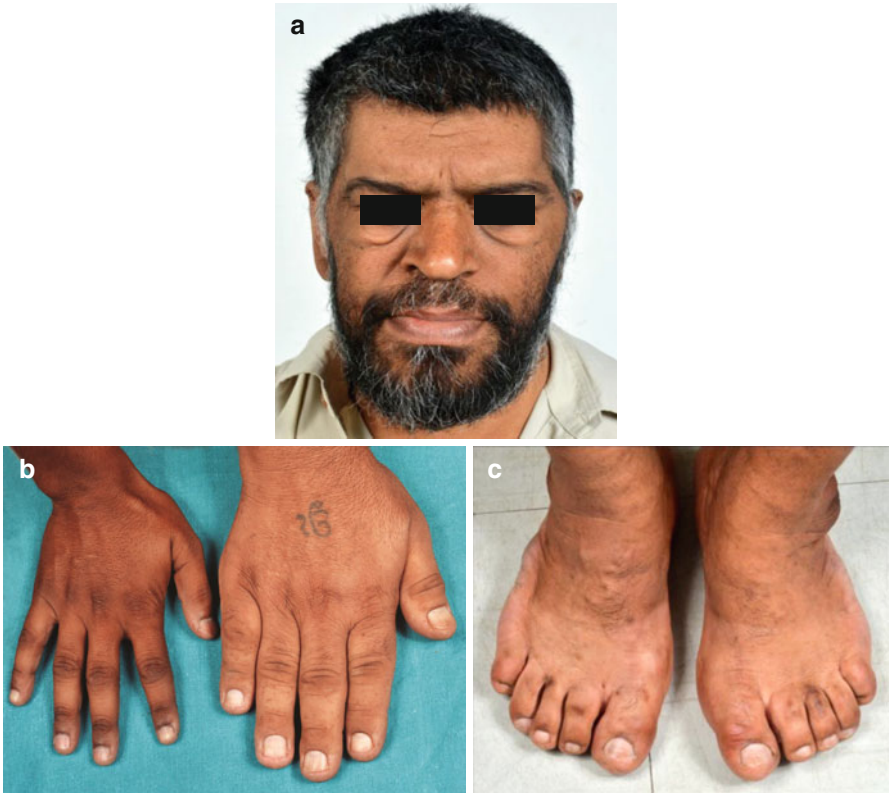

Fig. 1.2 (**a**) Coarse facial features, prominent supraorbital ridges, bulbous nose prognathism, and thick lips in a patient with acromegaly. (**b**) Enlargement of the hands in a patient with acromegaly (*left*) as compared to a normal individual (*right*). (**c**) Enlargement of the feet in the same patient with acromegaly

1.3 Clinical Rounds

1. **What is acromegaly?**

   Acromegaly is a Greek word meaning "akros" (extremity) and "megalos" (enlargement). Acral is a term pertaining to the outermost parts of the extremities (i.e., hands and feet) and face (i.e., supraorbital ridges, chin, nose, lips, and ears). It denotes enlargement of soft-tissue and osseous tissue in acral areas.

2. **What is "clinically active" acromegaly?**

   Acromegaly is said to be "clinically active" in the presence of worsening headache, hyperhidrosis, seborrhea, progressive soft tissue swelling, new-onset visual symptoms, arthralgia, compressive neuropathy, difficult to control hyperglycemia, and resistant hypertension.

3. **What are the causes of acromegaly with subtle facial features?**

Gradual alterations in facial features in a patient with acromegaly may not be appreciated for a long time, thereby causing a delay in diagnosis up to 8–10 years. By the time a diagnosis is made, facial features are too obvious. Disorders associated with subtle facial features of acromegaly are McCune–Albright syndrome (MAS), adolescent acromegaly (due to peripubertal growth spurt), mild acromegaly, concurrent thyrotoxicosis, fugitive acromegaly, and sarcopenia associated with poorly controlled diabetes or malignancy.

4. **What is fugitive acromegaly?**

Fugitive acromegaly is characterized by subtle features of acromegaly, predominantly raised prolactin, normal or mildly elevated GH, suppressible GH after glucose load, and marginally elevated insulin like growth factor 1 (IGF1). Intrinsic GH-like activity of prolactin along with marginally elevated IGF1 accounts for the subtle features of acromegaly. Fugitive acromegaly is commonly due to acidophil stem cell tumor which predominantly secretes prolactin along with small amounts of GH, with immunopositivity for both prolactin and GH in tumor tissue. These tumors are usually large, locally invasive, and resistant to dopamine agonist therapy.

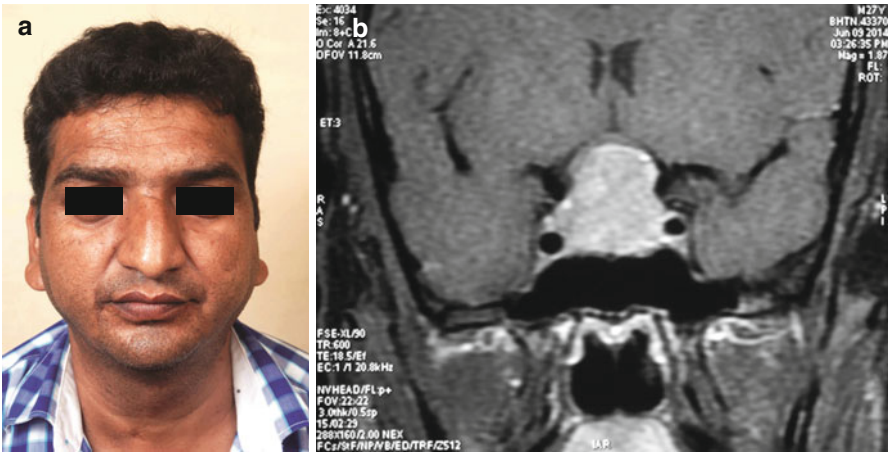

Fig. 1.3 (**a**) Coarse facial features in a patient with prolactinoma suggestive of fugitive acromegaly. (**b**) Coronal CEMR image showing homogenously enhancing sellar–suprasellar mass in the same patient ("figure of 8 appearance")

5. **What is pseudoacromegaly?**

Pseudoacromegaly is characterized by acromegaloid appearance without growth hormone excess. The causes include morbid obesity (severe insulin resistance), pachydermoperiostitis, hypothyroidism, insulin like growth factor 2 (IGF2)-

secreting tumors, insulinoma, and drugs like minoxidil and phenytoin. Pseudoacromegaly in patients with obesity and insulinoma due to the action of insulin on IGF1 receptor (specificity spillover). Presence of digital clubbing helps in differentiating pachydermoperiostitis from acromegaly. Minoxidil and phenytoin cause increased collagen growth and proliferation with abnormal cross-linking, resulting in an acromegaloid appearance. Pseudoacromegaly in patients with primary hypothyroidism is due to abnormal glycosaminoglycans (GAGs) deposition in the soft tissues.

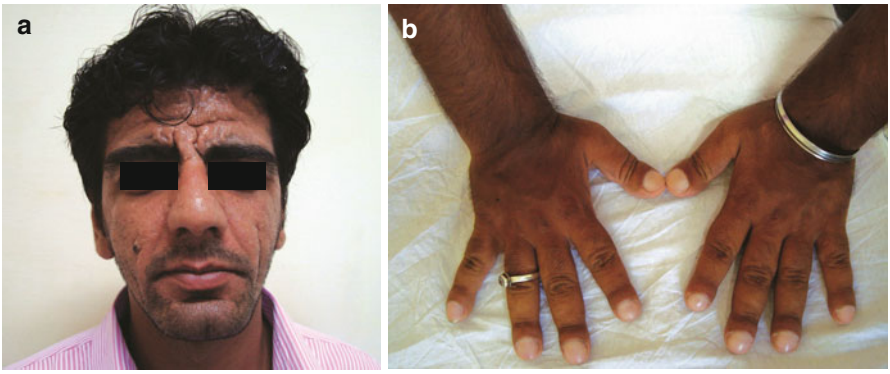

Fig. 1.4 (**a**) Pseudoacromegaly in a patient with pachydermoperiostitis. (**b**) Digital clubbing and broad hands in the same patient

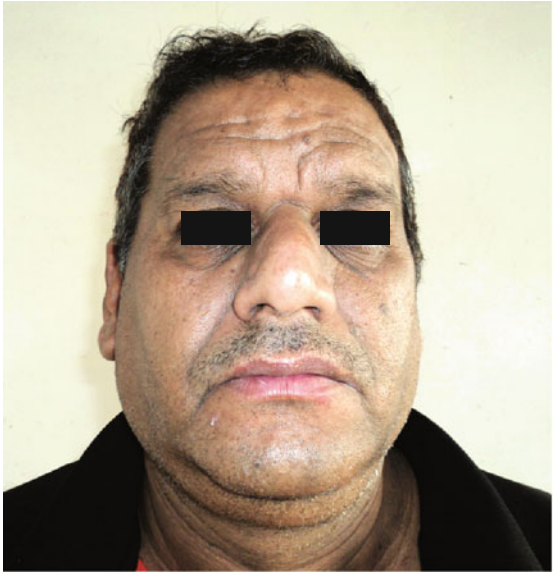

Fig. 1.5 Acromegaloid features in a patient with insulinoma

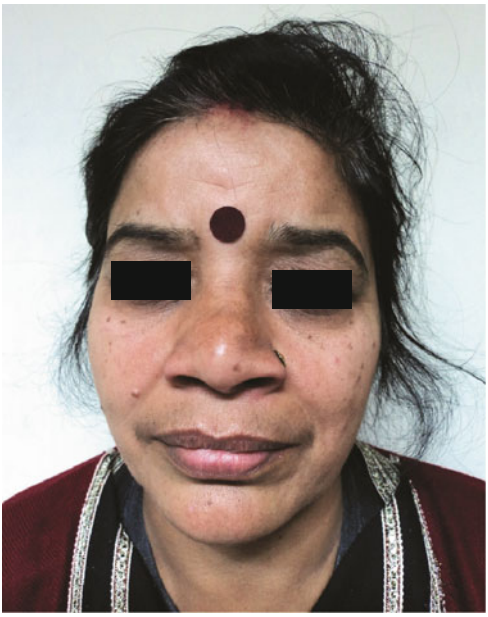

Fig. 1.6 Pseudoacromegaly due to phenytoin therapy

6. **What are the causes of acromegaly?**

The most common cause of acromegaly is somatotropinoma (99%). The tumor is usually a macroadenoma (in nearly 80%) as the disease is insidious in onset. In addition, paracrine effect of GH–IGF1 on tumor growth and genetic abnormalities like AIP gene mutation and PTTG overexpression contribute to macroadenoma. The table given below enlists the causes of acromegaly.

Causes of acromegaly
Primary growth hormone (GH) excess
Somatotropinoma (99%)
Rarely GH-secreting pancreatic islet cell tumor and lymphoma
Primary growth hormone releasing hormone (GHRH) excess
Eutopic (<1%)
Hypothalamic hamartoma, choristoma, ganglioneuroma
Ectopic (<1%)
Bronchial carcinoid, pancreatic islet cell tumor, small cell lung carcinoma, adrenal adenoma, medullary thyroid carcinoma, pheochromocytoma

7. **Why is ectopic GHRH-secreting tumor more common than ectopic GH-secreting tumor?**

GHRH has 44 amino acids and is a smaller peptide as compared to GH which has 191 amino acids. It is easier for dedifferentiated tumor cells to produce a peptide with a smaller number of amino acids; therefore, ectopic GHRH-secreting tumors are more common than ectopic GH-secreting tumors.

8. **When to consider the diagnosis of familial acromegaly?**

   The diagnosis of familial acromegaly should be considered in acromegalic patients with younger age of onset (<30 years), aggressive tumor behavior, presence or subsequent development of multiple endocrine neoplasia, or family history of pituitary tumor. Causes of familial acromegaly with autosomal dominant inheritance are Carney's complex, familial isolated pituitary adenoma (FIPA), and multiple endocrine neoplasia (MEN1, MEN4). Rarely, paraganglioma-associated *SDH* mutations can be associated with acromegaly. McCune–Albright syndrome is not a cause of familial acromegaly as it is due to postzygotic somatic mutation and not due to germ line mutation.

9. **What are the characteristics of aryl hydrocarbon receptor-interacting protein (AIP) gene mutation-related acromegaly?**

   Aryl hydrocarbon receptor-interacting protein (AIP) gene is responsible for ordered cell growth and proliferation in normal individuals. Loss-of-function mutation of the tumor suppressor gene AIP leads to dysregulation of the cell cycle and results in tumorigenesis. AIP gene mutation is responsible for 15–20% of cases of familial isolated pituitary adenoma (FIPA). Somatotropinoma and mixed GH- and prolactin-secreting tumor are the most common tumors associated with AIP mutations. The characteristics of AIP-related acromegaly are younger age of onset, family history of pituitary tumor, and aggressive and invasive adenoma refractory to treatment with somatostatin analogues. AIP-related mutations are also seen in prolactinoma, nonfunctioning pituitary adenoma, thyroid-stimulating hormone-secreting adenoma, and rarely corticotropinoma.

10. **Is there any correlation between clinical phenotype and histopathology of somatotropinoma?**

    Clinical and histological correlation among various subtypes of somatotropinomas is summarized in the table below.

Histological subtype	Hormone secreted	Clinical correlation
Densely granulated	GH	Mild disease Good response to treatment
Sparsely granulated	GH	Rapidly progressive Poor response to treatment
Mammosomatotropinoma	GH, PRL	Usually in children Gigantism
Acidophil stem cell adenoma	PRL, GH	Fugitive acromegaly Predominantly hyperprolactinemia

11. **How to define acro-gigantism?**

    Acromegaly is a disease of adults, but when GH excess occurs in children and adolescents before epiphyseal fusion, it results in acro-gigantism. It is defined as

the height of an individual > 97th percentile or 3SD above normal mean height for age or height >2SD above the mid-parental height with features of acromegaly.

12. **What are the causes of acro-gigantism?**

Growth hormone excess associated with familial syndrome usually results in acro-gigantism and the causes include familial isolated pituitary adenoma, multiple endocrine neoplasia type 1 and Carney's complex. In addition, McCune–Albright syndrome can also lead to acro-gigantism.

13. **Why are all adolescent with GH excess not acro-giants?**

Prepubertal GH–IGF1 excess is expected to result in acro-gigantism. However, only one-third of patients with GH excess during adolescence are acro-giants. Patients who develop acro-gigantism have relatively higher GH–IGF1 levels, normal thyroid function, and concurrent hypogonadism as compared to those who do not develop acro-gigantism. Children with McCune–Albright syndrome with precocious puberty who are untreated, and subsequently develop GH excess may not have acro-gigantism. Further, patients with coexisting hypochondroplasia may not develop acro-gigantism.

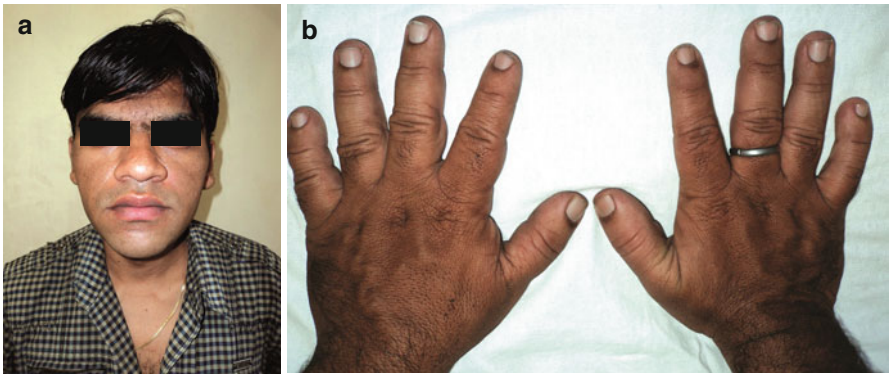

Fig. 1.7 (**a**) Characteristic facial features of acromegaly in an adolescent who had hypochondroplasia, but without acro-gigantism. (**b**) Short stout hands with soft tissue overgrowth in the same patient

14. **What are the characteristics of acromegaly associated with McCune–Albright syndrome?**

The characteristic features of acromegaly associated with McCune–Albright syndrome include younger age of onset, cafe-au-lait macule, fibrous dysplasia, hyperprolactinemia (70%), concurrent endocrinopathies, and lack of demonstrable pituitary adenoma in nearly half of the patients. Medical therapy is preferred in these patients as surgery is difficult, and radiotherapy is associated with an increased risk of osteosarcoma.

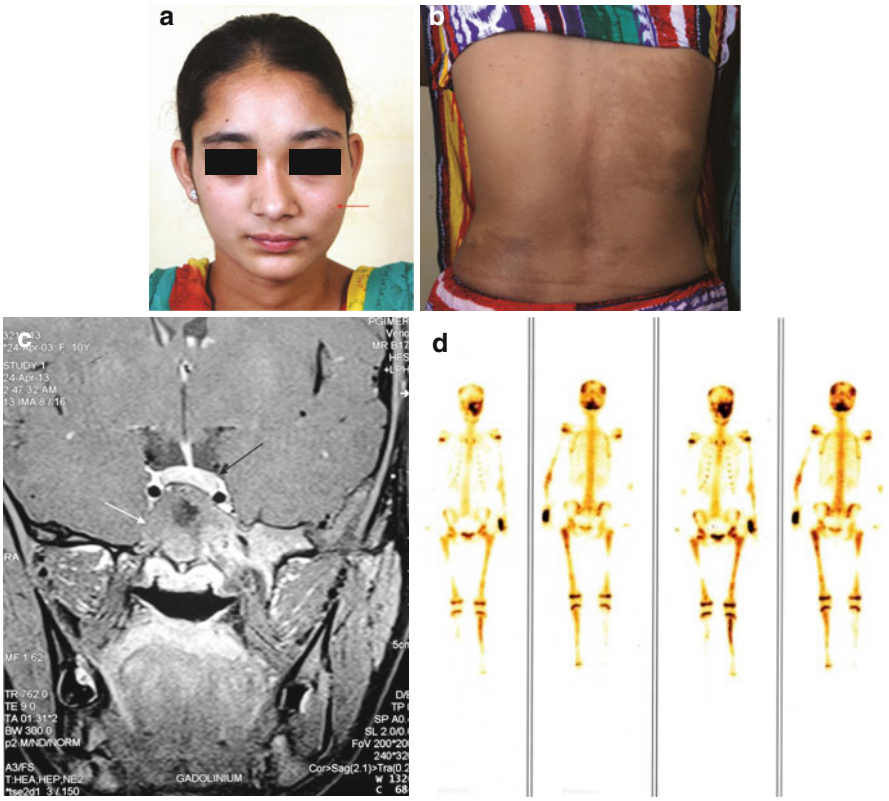

Fig. 1.8 (**a**) A 12-year-old girl with McCune–Albright syndrome who had precocious puberty, acro-gigantism, and hyperthyroidism. Facial asymmetry (*arrow*) due to fibrous dysplasia is also seen. (**b**) Cafe-au-lait macule in the same patient with McCune–Albright syndrome. (**c**) T1W CEMR coronal image showing normal pituitary gland (*black arrow*) in the same patient. Note upward convexity of sellar floor due to sphenoid bone fibrous dysplasia (*white arrow*). (**d**) ^{99m}Tc MDP bone scan showing increased tracer uptake in skull bones in the same patient

15. What are the unusual presentations of acromegaly?

Majority of patients with acromegaly are either diagnosed incidentally or during evaluation for headache, visual symptoms, acral enlargement, arthralgia, and uncontrolled diabetes. The unusual presentations of acromegaly are malocclusion of jaw, diabetic ketoacidosis, pituitary apoplexy, CSF rhinorrhea, facial asymmetry (fibrous dysplasia in McCune–Albright syndrome), tonsillomegaly, recurrent nasal obstruction (nasal polyp), severe hirsutism, entrapment neuropathy, dilated cardiomyopathy, cutis verticis gyrata, and frontal lobe syndrome (antesellar extension of tumor or anterior cerebral artery spasm due to apoplexy).

Fig. 1.9 Facial asymmetry (due to fibrous dysplasia) as a presenting manifestation of an acro-giant with McCune–Albright syndrome

16. **What are the emergencies in a patient with acromegaly?**

Patients with acromegaly can present in emergency due to pituitary apoplexy, subarachnoid hemorrhage (rupture of intracranial arteriovenous malformations), status epilepticus (raised intracranial tension, hyponatremia, and cerebral invasion), paraplegia (intervertebral disc prolapse), accelerated hypertension, diabetic ketoacidosis, gastrointestinal bleed (colonic polyp/carcinoma), cardiac arrhythmias, and acromegalic cardiomyopathy.

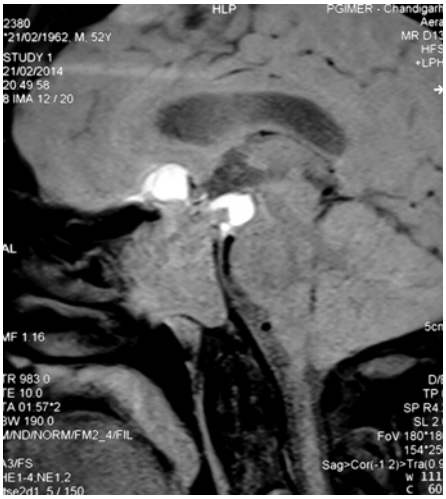

Fig. 1.10 T1W noncontrast sagittal MR image demonstrating pituitary macroadenoma with marked infra- and antesellar extension. Hyperintense areas are suggestive of hemorrhage within the tumor

17. **What are the unusual signs in patients with acromegaly?**

The unusual signs in patients with acromegaly include cutis verticis gyrata ("sulci and gyri"-like appearance on the scalp), facial asymmetry (fibrous dysplasia due to McCune–Albright syndrome and osteitis fibrosa cystica due to primary hyperparathyroidism, MEN1), tonsillomegaly, acromegalic rosary, orchidomegaly, gynecomastia, osteoma and tarsal tunnel syndrome.

18. **What are the causes of cutis verticis gyrata?**

Cutis verticis gyrata is not a specific feature of acromegaly, but is also seen in patients with neurofibroma, pachydermoperiostitis**,** melanocytic nevi, myxedema, and amyloidosis. The "cerebral convolution"-like appearance in acromegaly is an adaptive response to accommodate excessive soft tissue overgrowth in a limited space under the tight scalp fascia.

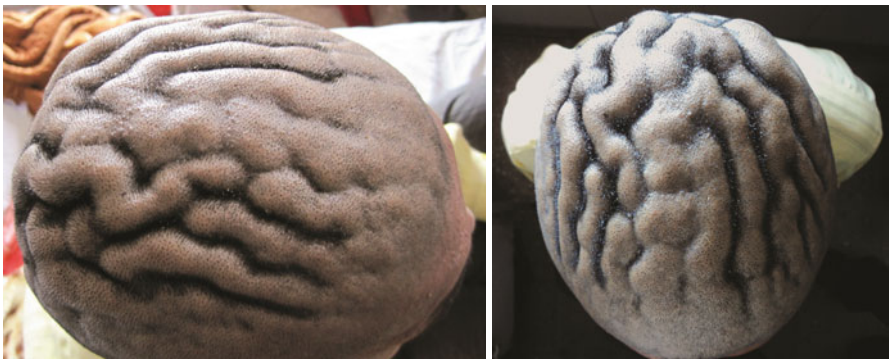

Fig. 1.11 Cutis verticis gyrata in a patient with acromegaly

19. **What are the causes of headache in acromegaly?**

Patients with acromegaly having microadenomas or macroadenomas can present with headache. In microadenomas, it is due to increased intrasellar pressure because of tumor growth in a closed space. In macroadenomas, headache is caused by stretching of the dura (supplied by ophthalmic division of the trigeminal nerve) due to suprasellar extension of tumor or direct involvement of the trigeminal nerve due to cavernous sinus invasion. Other causes of headache related to acromegaly per se, irrespective of tumor size, include calvarial thickening leading to periosteal stretch, osteomas, recurrent sinusitis, and secretion of putative algesic peptides by the tumor tissue. Causes of acute-onset severe headache in a patient with acromegaly include pituitary apoplexy, aneurysmal rupture, or rarely, raised intracranial tension due to hydrocephalus.

20. **What are the causes of macroglossia?**

Macroglossia is considered when the tongue extends beyond the alveolar ridge in the resting state. It is suggested by the presence of indentation marks on the tongue. Causes of macroglossia include acromegaly, primary hypothyroidism, Down's syndrome, amyloidosis, hemangioma, lymphangioma, and tongue neoplasms.

21. **What are the oral manifestations of acromegaly?**

Oral manifestations in a patient with acromegaly include prognathism, thick fleshy lips, increased spacing between teeth, malalignment of jaw, macroglossia and tonsillomegaly. In addition, thickened lamina dura may be present on imaging. Patients with acromegaly may have bony swellings in the oral cavity due to fibrous dysplasia or osteitis fibrosa cystica, when associated with McCune-Albright syndrome and MEN1, respectively.

22. **What are the cutaneous manifestations of acromegaly?**

The cutaneous manifestations in a patient with acromegaly include hyperhidrosis, seborrhea, hirsutism, acanthosis nigricans, skin tags (>3 correlates with the presence of colonic polyps), hyperpigmentation and cutis verticis gyrata. Patients with acromegaly may have cafe-au-lait macules when associated with McCune-Albright syndrome and lipoma, angiofibroma and collagenoma when associated with MEN1 syndrome.

23. **Why are hands warm and moist in patients with acromegaly?**

GH promotes peripheral deiodinase activity and increases T_4 to T_3 neogenesis. This is responsible for the increased adrenergic sensitivity manifesting clinically as warm and moist hands. The direct effect of GH per se, on sweat glands, also contributes. The effect of GH on pilosebaceous units explains the presence of seborrhea in patients with acromegaly.

24. **What are the causes of goiter in acromegaly?**

Goiter is present in 70–80% of patients with acromegaly. Thyroid enlargement may be diffuse or multinodular and is usually associated with normal thyroid function; however, 4–14% of patients may have hyperthyroidism. The causes of goiter in acromegaly include GH–IGF1-mediated growth and proliferation of thyroid follicular cells, McCune–Albright Syndrome, GH and TSH co-secreting adenoma, and medullary thyroid carcinoma with ectopic GHRH secretion. Solitary nodule in a patient with acromegaly should raise the suspicion of papillary thyroid cancer as it is one of the common cancers associated with acromegaly.

25. **What is the effect of GH on thyroid function?**

GH potentiates T_4 to T_3 neogenesis by the activation of 5′-monodeiodinase type 1, decreases thyroxine-binding globulin, and inhibits TSH. Suppression of TSH is mediated by increased somatostatin tone associated with GH excess.

26. **Why do patients with acromegaly have arthralgia?**

Arthralgia and osteoarthritis are common in patients with acromegaly with a prevalence of 50–70%. GH–IGF1 excess results in uneven articular chondrocyte proliferation and matrix production in a limited joint space followed by cartilage destruction leading to arthralgia and osteoarthritis. In addition, synovial hypertrophy and ligament laxity lead to joint instability.

27. **Why do patients with acromegaly have hypertension?**

Hypertension is present in 35–50% of patients with acromegaly. Causes of hypertension include extracellular volume expansion due to the anti-natriuretic action of GH–IGF1 on renal tubules, increased left ventricular mass, insulin resistance/hyperinsulinemia, production of digitalis-like substances, and altered sympathetic activity. Renin–angiotensin–aldosterone axis is suppressed in patients with acromegaly due to volume expansion. Concurrent obstructive sleep apnea also exacerbates hypertension. Diuretics are drug of choice for the management of hypertension in patients with acromegaly.

28. **Why do patients with acromegaly have diabetes?**

Dysglycemia is present in approximately 50% of patients with acromegaly (diabetes 10–15% and prediabetes 20–40%). It is more prevalent in those who have long duration of disease, higher GH levels, and family history of diabetes. Diabetes in acromegaly occurs despite GH-mediated β-cell hyperplasia. GH antagonizes the action of insulin at the liver, skeletal muscle, and adipocytes, and this results in increased hepatic glucose output due to augmented glycogenolysis and gluconeogenesis, reduced uptake of glucose into muscle and adipocytes, and increased lipolysis. Hyperglycemia associated with acromegaly is frequently severe and difficult to treat. Therefore, patients with resistant diabetes should be evaluated for acromegaly.

29. **What are the mechanisms for GH-mediated insulin resistance?**

Acromegaly is characterized by chronic GH and IGF1 excess, and these hormones have opposing effects on glucose metabolism; IGF1 has insulin like effects, whereas GH has insulin-antagonistic properties; the effects of GH predominates over IGF1. IGF1 acts on IGF1/insulin receptor and stimulates insulin-signaling pathway, while GH acts via its own receptor and interferes with the insulin-signaling pathway. Phosphatidylinositol 3-kinase (PI3K) and IRS-1 are involved in post-receptor insulin- signaling pathway. GH increases the p85 subunit of phosphatidylinositol 3-kinase (PI3K), which results in imbalance

between p85 and p110 subunits of PI3K, and consequently reduced PI3K signaling. Further, GH increases the serine phosphorylation of IRS-1, thereby preventing its association with the insulin receptor. GH also induces suppressor of cytokine signaling (SOCS) pathway, which prevents tyrosine phosphorylation of IRS-1 and results in insulin resistance. GH also decreases the expression of insulin-sensitizing adipokines like adiponectin and visfatin. In addition, GH promotes lipolysis and increases the serum levels of non-esterified fatty acids, resulting in worsening of insulin resistance.

30. **What are the cardiovascular manifestations in acromegaly?**

Cardiovascular manifestations in acromegaly include cardiomyopathy, heart failure, asymmetrical septal hypertrophy, arrhythmias, and coronary artery disease. Diastolic dysfunction is the earliest abnormality in acromegalic cardiomyopathy, followed by systolic dysfunction and eventually heart failure which is characteristically associated with increased left ventricular muscle mass. Coronary artery disease in acromegaly is due to dyslipidemia, increased procoagulant activity and concurrent diabetes and hypertension. Arrhythmias are present in 40% of patients with acromegaly and include atrial fibrillation, supraventricular tachycardia, bundle branch block, and ventricular ectopy and are usually related to cardiomyopathy. In addition, bradycardia can occur in these patients with the use of octreotide.

31. **Why is there increased cardiovascular risk in acromegaly?**

Cardiovascular disease is the major cause of mortality (60%) in patients with acromegaly. Increased cardiovascular risk is due to hypertension, obstructive sleep apnea, increased left ventricular muscle mass, atherogenic lipid profile, hyperfibrogenemia, increased plasminogen activator inhibitor type 1 (PAI-1), and insulin resistance/hyperinsulinemia. These effects are mediated through GH–IGF1 excess and underscore the need for eusomatotropinemia in these patients.

32. **Why do patients with acromegaly have obstructive sleep apnea?**

Acromegaly is associated with obstructive sleep apnea (OSA) in 40–50% of patients. OSA is due to naso–pharyngo–laryngeal tissue overgrowth, nasal polyps, and macroglossia because of GH–IGF1 excess. In addition, direct effect of GH on the respiratory center causes central sleep apnea. OSA may not remit even after curative surgery.

33. **What are the possibilities when a patient with acromegaly presents with weight loss?**

Patients with acromegaly commonly present with weight gain due to increase in lean muscle mass because of the anabolic effects of GH. However, they may present with weight loss if associated with uncontrolled diabetes, thyrotoxicosis and malignancy. Thyrotoxicosis in acromegaly is due to GH excess per se (4–14%), GH and TSH co-secreting adenoma, or McCune–Albright syndrome. Acromegaly is associated with an increased risk of malignancy of colon, breast, and thyroid.

34. **What are the causes of hirsutism in acromegaly?**

Hirsutism is present in nearly half of the patients with acromegaly. It is due to direct effect of GH–IGF1 on pilosebaceous units and GH-mediated hyperandrogenemia. Hyperandrogenemia is due to decreased SHBG, insulin resistance/hyperinsulinemia, and increased ovarian steroidogenesis. In addition, hyperprolactinemia which is present in 30% of patients with acromegaly can also result in increased androgen production. Hirsutism in these patients is invariably accompanied with menstrual irregularities.

35. **Why do patients with acromegaly have hyperprolactinemia?**

Nearly 30% of patients with acromegaly have hyperprolactinemia. It can be due to stem cell adenoma, mammosomatotropinoma, mixed cell adenoma and stalk hyperprolactinemia. Lactotropes and somatotropes share a common origin during pituitary ontogenesis and this explains the development of stem cell adenoma and mammosomatotropinoma.

36. **What are the causes of menstrual irregularities in acromegaly?**

Menstrual irregularities are present in 40–80% of women with acromegaly and usually present as oligomenorrhea, secondary amenorrhea, and rarely menorrhagia. These manifestations are attributed to low gonadotropins due to mass effect, hyperprolactinemia, secondary polycystic ovarian disease, hyperandrogenemia and hypothyroidism. Despite hypogonadism, these women have endometrial hyperplasia due to the direct effect of GH on endometrial growth and proliferation.

37. **Can patients with acromegaly have menstrual irregularities and galactorrhea despite microadenoma and normal prolactin?**

Menstrual irregularities can occur even in patients with microadenoma and normal prolactin. This can be explained by the presence of hyperandrogenemia due to insulin resistance/hyperinsulinemia, direct GH–IGF1 effect on ovarian steroidogenesis, and decreased SHBG. GH is homologous to prolactin and has intrinsic "prolactin-like activity" (specificity spillover) which explains galactorrhea in some women with acromegaly despite normal prolactin.

38. **What are the causes of endometrial hyperplasia despite amenorrhea?**

The causes of endometrial hyperplasia (endometrial thickness >10 mm) despite amenorrhea are acromegaly, polycystic ovarian disease, and drugs like tamoxifen. Endometrial hyperplasia in acromegaly is due to the direct proliferative effect of GH–IGF1 on the endometrium, despite low gonadotropins.

39. **What is the difference in the pathogenesis of polycystic ovarian disease due to acromegaly from classical polycystic ovarian disease?**

Secondary polycystic ovarian disease (PCOD) is common in patients with acromegaly. PCOD related to acromegaly is due to the direct effects of GH–

IGF1 on ovary and is independent of LH as opposed to classical polycystic ovarian disease where LH plays an important role in thecal growth and proliferation.

40. **What are the peripheral neurological manifestations related to GH–IGF1 excess?**

Peripheral neurological manifestations associated with GH–IGF1 excess are entrapment neuropathy (eg., carpal tunnel and tarsal tunnel syndrome), peripheral neuropathy, compressive myelopathy (due to disc prolapse) and lumbar canal stenosis. Thickened peripheral nerve is also a feature of acromegaly and is due to perineural deposition of glycosaminoglycans (GAGs).

41. **Does brain size increase in acromegaly?**

Brain parenchymal tissue does not increase in size in response to GH–IGF1 excess. Nevertheless, patients with acromegaly have increased risk of cerebrovascular accidents, cerebral aneurysms, and radiation-induced brain damage (RIBD) due to detrimental effects of GH–IGF1 excess on cerebral vasculature.

42. **Do patients with acromegaly have increased prevalence of cerebral aneurysms?**

Yes. The available literature points to an increased prevalence of cerebral aneurysms (7–10%) in patients with acromegaly. Altered ratio of type-III to type-I collagen due to GH–IGF1 excess leads to degeneration of vessel wall and consequently results in the development of aneurysms. The cerebral aneurysms in patients with acromegaly are usually located in the internal carotid artery and rarely in the vertebrobasilar artery.

43. **Can patients with acromegaly have proximal muscle weakness?**

Yes. GH–IGF1 is required for the development and maintenance of lean muscle mass. However, acromegaly may be associated with proximal myopathy due to atrophy of type 2 muscle fibers with relative hypertrophy of type 1 fibers. In addition, hyperphosphatemia may also contribute to muscle weakness. Patients with acromegaly who have myelo-radiculopathy may also manifest proximal muscle weakness.

44. **What are the causes of anemia in acromegaly?**

GH plays a permissive role in erythropoiesis. Therefore, anemia in a patient with acromegaly is unusual and requires evaluation. The causes of anemia in acromegaly are gastrointestinal bleed due to adenomatous polyp, colonic carcinoma, acid peptic disease (MEN1, Zollinger–Ellison syndrome), and malabsorption due to megacolon and bacterial stasis (blind-loop syndrome). In addition, hypothyroidism, hypogonadism, and hypocortisolism may also contribute to the development of anemia.