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ETIOPATHOGENESIS AND CLINICAL MANIFESTATIONS OF ACROMEGALY: PATHOPHYSIOLOGICAL MECHANISMS AND SYSTEMIC COMPLICATIONS

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Abstract

Acromegaly is a rare, chronic endocrine disorder characterized by prolonged exposure to excessive growth hormone (GH) and insulin-like growth factor-1 (IGF-1), most commonly resulting from a GH-secreting pituitary adenoma. Despite its insidious onset, acromegaly is associated with substantial morbidity and increased mortality, primarily due to cardiovascular, metabolic, respiratory, and neoplastic complications. A delayed diagnosis remains a major clinical challenge, as early manifestations are often subtle and progress slowly over years.The etiopathogenesis of acromegaly involves dysregulation of the hypothalamic–pituitary–somatic axis, leading to autonomous GH secretion and subsequent elevation of circulating IGF-1. At the molecular level, somatic mutations, particularly in the *GNAS* gene, play a crucial role in pituitary adenoma development and hormonal hypersecretion. Persistent activation of GH and IGF-1 signaling pathways induces widespread anabolic, mitogenic, and anti-apoptotic effects, resulting in tissue overgrowth, organomegaly, and structural remodeling of multiple organ systems.Clinically, acromegaly presents with a broad spectrum of manifestations affecting the musculoskeletal, cardiovascular, respiratory, metabolic, and neurological systems. Characteristic phenotypic features include acral enlargement, facial dysmorphism, and soft tissue hypertrophy, while systemic complications such as cardiomyopathy, arterial hypertension, insulin resistance, type 2 diabetes mellitus, obstructive sleep apnea, and increased risk of malignancies significantly contribute to disease burden. The heterogeneity of clinical presentation underscores the importance of a multidisciplinary approach to diagnosis and management.

This review provides a comprehensive overview of the etiopathogenetic mechanisms underlying acromegaly and highlights the systemic nature of its clinical manifestations. A deeper understanding of the pathophysiological processes involved is essential for early recognition, risk stratification, and optimization of therapeutic strategies aimed at reducing long-term complications and improving patient outcomes.

Keywords

Acromegaly; Growth hormone; Insulin-like growth factor-1; Pituitary adenoma; GH–IGF-1 axis; Clinical manifestations; Multisystem complications

Acromegaly is a rare, chronic endocrine disorder caused by persistent hypersecretion of growth hormone (GH) and its peripheral mediator insulin-like growth factor-1 (IGF-1). In the majority of cases, the condition arises from a GH-secreting pituitary adenoma, leading to prolonged exposure of peripheral tissues to elevated hormone levels. The insidious onset and slow progression of the disease frequently result in substantial diagnostic delays, during which patients develop multiple systemic comorbidities and experience a significant deterioration in quality of life. The pathophysiological consequences of chronic GH and IGF-1 excess extend far

beyond somatic overgrowth and include profound metabolic, cardiovascular, respiratory, and musculoskeletal alterations. These hormonal abnormalities promote tissue hypertrophy, organomegaly, and structural remodeling, ultimately contributing to increased morbidity and premature mortality. Despite advances in biochemical assays for GH and IGF-1 and improvements in pituitary imaging techniques, challenges in early diagnosis and comprehensive morbidity assessment remain significant. Clinical manifestations of acromegaly are heterogeneous and often evolve gradually, complicating timely recognition. Patients may present with characteristic acral and facial changes, as well as systemic complications such as cardiomyopathy, arterial hypertension, insulin resistance, diabetes mellitus, obstructive sleep apnea, and an increased risk of neoplasia. The broad spectrum of clinical involvement highlights the systemic nature of the disease and underscores the need for a thorough understanding of its etiopathogenetic mechanisms.

This review aims to provide an in-depth overview of the etiopathogenesis of acromegaly and to systematically describe its clinical manifestations, with particular emphasis on the underlying pathophysiological mechanisms and the development of multisystem complications.

Etiology and Pathogenesis of Acromegaly

Acromegaly is predominantly caused by autonomous hypersecretion of growth hormone (GH) from a pituitary somatotroph adenoma, accounting for approximately 95% of cases. These adenomas are usually benign, slow-growing tumors originating from somatotroph cells of the anterior pituitary gland. In rare instances, acromegaly may result from ectopic secretion of GH or growth hormone–releasing hormone (GHRH) by non-pituitary tumors, including neuroendocrine tumors of the pancreas, lung, or hypothalamus, leading to secondary pituitary hyperplasia.

At the molecular level, the pathogenesis of pituitary adenomas in acromegaly involves genetic and epigenetic alterations that promote somatotroph cell proliferation and dysregulated hormone secretion. Activating mutations of the *GNAS* gene, which encodes the stimulatory Gsα subunit of adenylate cyclase, are among the most frequently identified genetic abnormalities. These mutations result in constitutive activation of cyclic adenosine monophosphate (cAMP) signaling, driving excessive GH synthesis and secretion independent of physiological regulatory mechanisms. Additional molecular contributors include alterations in cell cycle regulators, transcription factors, and signaling pathways involved in pituitary cell differentiation and survival.

Physiologically, GH secretion is tightly regulated by the balance between hypothalamic growth hormone–releasing hormone (GHRH) and somatostatin. In acromegaly, this regulatory feedback loop is disrupted by autonomous GH secretion, leading to persistently elevated circulating GH levels and subsequent hepatic overproduction of insulin-like growth factor-1 (IGF-1). IGF-1 mediates many of the peripheral effects of GH through endocrine, paracrine, and autocrine mechanisms, exerting potent anabolic, mitogenic, and anti-apoptotic actions on multiple tissues. Chronic activation of the GH–IGF-1 axis induces widespread structural and functional changes across organ systems. Binding of GH and IGF-1 to their respective receptors activates intracellular signaling cascades, including the Janus kinase–signal transducer and activator of transcription (JAK–STAT), phosphoinositide 3-kinase (PI3K)–Akt, and mitogen-activated protein kinase (MAPK) pathways. Sustained stimulation of these pathways promotes

cellular hypertrophy, hyperplasia, and extracellular matrix remodeling, leading to tissue overgrowth, organomegaly, and progressive organ dysfunction.

Furthermore, prolonged exposure to elevated GH and IGF-1 levels results in significant metabolic dysregulation. GH-induced insulin resistance, mediated by impaired insulin signaling and increased lipolysis, contributes to glucose intolerance and the development of type 2 diabetes mellitus. Concurrently, IGF-1 exerts insulin-like effects that partially counterbalance GH-induced metabolic alterations, creating a complex and dynamic metabolic milieu. The net effect is a predisposition to metabolic syndrome, dyslipidemia, and increased cardiovascular risk. In addition to endocrine and metabolic effects, GH and IGF-1 excess influences cardiovascular structure and function through myocardial hypertrophy, interstitial fibrosis, and altered vascular reactivity. These changes culminate in acromegalic cardiomyopathy, characterized by concentric ventricular hypertrophy, diastolic dysfunction, and, in advanced stages, systolic heart failure. Similar mechanisms underlie respiratory, musculoskeletal, and soft tissue involvement, highlighting the multisystemic nature of acromegaly.

Clinical Manifestations and Complications of Acromegaly

The clinical presentation of acromegaly is highly heterogeneous and evolves gradually over many years, reflecting the chronic effects of excessive growth hormone (GH) and insulin-like growth factor-1 (IGF-1) on multiple organ systems. As a result, early symptoms are often nonspecific, leading to delayed diagnosis and the development of advanced systemic complications at the time of clinical recognition.

Somatic and Musculoskeletal Manifestations

One of the hallmark features of acromegaly is progressive somatic overgrowth, particularly affecting acral regions. Patients typically develop enlargement of the hands and feet, increased shoe and ring size, and characteristic facial changes such as frontal bossing, prognathism, widened nasal bridge, macroglossia, and thickened lips. Soft tissue hypertrophy contributes to coarse facial features and skin thickening, often accompanied by hyperhidrosis and oily skin. Musculoskeletal involvement is common and represents a major source of morbidity. Chronic exposure to GH and IGF-1 leads to joint cartilage overgrowth, ligament thickening, and abnormal bone remodeling, resulting in acromegalic arthropathy. Patients frequently report joint pain, stiffness, reduced range of motion, and functional impairment, most commonly affecting the spine, hips, knees, and shoulders. Vertebral enlargement and degenerative changes may cause kyphosis, back pain, and increased risk of spinal canal stenosis.

Cardiovascular Manifestations

Cardiovascular complications are the leading cause of increased mortality in patients with acromegaly. Excess GH and IGF-1 exert direct and indirect effects on the myocardium and vascular system, promoting myocardial hypertrophy, interstitial fibrosis, and impaired ventricular relaxation. These changes give rise to acromegalic cardiomyopathy, which typically progresses from concentric left ventricular hypertrophy and diastolic dysfunction to systolic dysfunction and heart failure in advanced disease. Arterial hypertension is highly prevalent and results from increased sodium retention, expanded plasma volume, endothelial dysfunction, and

enhanced vascular tone. Additionally, patients are at increased risk of arrhythmias, valvular heart disease, and accelerated atherosclerosis, further contributing to cardiovascular morbidity.

Respiratory Manifestations

Respiratory involvement in acromegaly is primarily related to soft tissue hypertrophy of the upper airway, macroglossia, and craniofacial structural changes. Obstructive sleep apnea (OSA) is highly prevalent and contributes significantly to daytime somnolence, impaired cognitive function, and cardiovascular complications. Thoracic cage deformities, respiratory muscle dysfunction, and reduced lung compliance may further impair respiratory function, leading to restrictive ventilatory defects.

Metabolic and Endocrine Complications

Metabolic disturbances are common in acromegaly and are largely driven by GH-induced insulin resistance. GH antagonizes insulin action at the hepatic and peripheral tissue levels, leading to impaired glucose tolerance and the development of type 2 diabetes mellitus in a substantial proportion of patients. Dyslipidemia and features of metabolic syndrome frequently coexist, compounding cardiovascular risk.

Although IGF-1 possesses insulin-like properties, its metabolic effects are insufficient to counterbalance the diabetogenic actions of chronic GH excess. Additional endocrine abnormalities may include hypopituitarism due to tumor mass effect or treatment-related damage, as well as altered gonadal function resulting in menstrual irregularities, infertility, and sexual dysfunction.

Gastrointestinal and Neoplastic Complications

Patients with acromegaly exhibit an increased risk of gastrointestinal polyps and malignancies, particularly colorectal cancer. The mitogenic and anti-apoptotic properties of IGF-1 are thought to play a central role in tumorigenesis by promoting cellular proliferation and inhibiting programmed cell death. Consequently, regular screening for colorectal neoplasia is recommended as part of long-term disease management.

Neurological Manifestations

Neurological symptoms may arise from both hormonal effects and local tumor expansion. Headaches are common and may be related to increased intracranial pressure or dural stretching. Visual field defects, particularly bitemporal hemianopia, can occur due to compression of the optic chiasm by the pituitary adenoma. Peripheral neuropathies, such as carpal tunnel syndrome, are frequent and result from soft tissue overgrowth and nerve compression.

Impact on Quality of Life

Beyond organ-specific complications, acromegaly profoundly affects patients' quality of life. Physical disfigurement, chronic pain, fatigue, psychological distress, and social stigmatization contribute to reduced emotional well-being and functional capacity. Even after biochemical

control is achieved, some complications and QoL impairments may persist, highlighting the importance of early diagnosis and comprehensive, multidisciplinary management.

Conclusion: Acromegaly is a chronic multisystem endocrine disorder caused by sustained excess of growth hormone and insulin-like growth factor-1, most often due to a growth hormone–secreting pituitary adenoma. The insidious progression of the disease results in delayed diagnosis and the development of significant systemic complications that contribute to increased morbidity and mortality. Persistent activation of the growth hormone–IGF-1 axis leads to widespread structural and metabolic alterations, affecting the cardiovascular, metabolic, respiratory, musculoskeletal, and neoplastic systems. These changes not only impair organ function but also markedly reduce patients' quality of life. Therefore, a thorough understanding of the underlying etiopathogenetic mechanisms is essential for timely recognition and comprehensive clinical assessment. Early diagnosis and individualized, multidisciplinary management are key to improving long-term outcomes in acromegaly. Continued advances in diagnostic tools and therapeutic strategies, together with optimized comorbidity management, are crucial to reducing disease burden and improving survival and quality of life in affected patients.

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