Early descriptions of acromegaly and gigantism and their historical evolution as clinical entities

Historical vignette

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Giants have been a subject of fascination throughout history. Whereas descriptions of giants have existed in the lay literature for millennia, the first attempt at a medical description was published by Johannes Wier in 1567. However, it was Pierre Marie, in 1886, who established the term “acromegaly” for the first time and established a distinct clinical diagnosis with clear clinical descriptions in 2 patients with the characteristic presentation. Multiple autopsy findings revealed a consistent correlation between acromegaly and pituitary enlargement. In 1909, Harvey Cushing postulated a “hormone of growth” as the underlying pathophysiological trigger involved in pituitary hypersecretion in patients with acromegaly. This theory was supported by his observations of clinical remission in patients with acromegaly in whom he had performed hypophysectomy. In this paper, the authors present some of the early accounts of acromegaly and gigantism, and describe its historical evolution as a medical and surgical entity.

KEY WORDS • acromegaly • gigantism • historical vignette • pituitary tumor

ACROMEGALIC individuals and giants have been the subject of fascination for millennia. Whereas there have been a multitude of descriptions in the lay literature since the beginnings of the written word, the first scientific description was probably made by Dutch physician and occultist Johannes Wier. His medical description of a giantess was published in 1567 in the *Medicarum Observationum.*48 Further descriptions surfaced in the late 18th and early 19th centuries by Noel (1779), Saucerotte (1801), Gall (1810), and Magendie (1839).15,24,27,36 In 1835, French dermatologist Jean-Louis-Marc Alibert described “Geant scrofuleux” in his monograph on dermatological disorders.1 In 1857, W. O. Chalk described a case of pathological dislocation of the jaw secondary to macroglossia in a patient with acromegaly.9 In 1864, the Italian neurologist Andre Verga described “prosopectasia” (widening of the face), while in 1868, Lombroso described “macrosomia.”25,26,45 These were followed by case descriptions by Friedreich in 1868 and Henrot in 1877, the latter including an autopsy report in which a 45 × 30–mm tumor in the position of the pituitary body was described.14,20,21 Brigidi, in 1877, described the case of the Italian actor Ghirlenzoni, stating: … unfortunately, he could not speak clearly, on account of the excessive size of his tongue … the rest of the face had more the appearance of an ape than a man. It was lengthened, with very marked prognathism, flattened and indented laterally, as if the cheeks had been elevated by a blow from the hatchet on each side.7,8

Taruffi described the skeletal deformities associated with acromegaly in 1877.41,42 A series of descriptions were to follow during the late 19th century.10,11,18,19,24,46 Even though multiple descriptions of this condition were reported by other physicians, the term “acromegaly” did not exist until 1886 when Pierre Marie defined the disease in his classic essay titled “Sur deux cas d’acromégalie; hypertrophie singulièere non congénitale des extrémités supérieures, inférieures et céphalique.”29

Pierre Marie: Establishment of Acromegaly as a Diagnosis

Despite early descriptions of acromegallic patients, there was no consensus on a unifying underlying diagnosis. Early in the 19th century, the concept of an endocrine system was not yet discovered. Therefore, most physicians at that time attributed the clinical findings of acromegaly to manifestations of other diseases such as Paget disease, myxedema, tuberculosis, syphilis, rheumatism, or gout. It was not until 1885 when Pierre Marie described 2 cases of an unusual noncongenital hypertrophy of the head and the upper and lower extremities, which were subsequently published in 1886.29 It was in this manuscript that the term “acromegaly” was first coined, and where it was
deemed a distinct clinical disease (also known as “Marie’s malady”). These 2 cases were observed in Professor Charcot’s clinic at the Salpêtrière Hospital in Paris.

Marie’s first case was that of a 37-year-old woman who had not sought medical attention before, but who had developed amenorrhea and headaches at the age of 24 years (Fig. 1). Describing his findings, he stated:

It was at the age of twenty-four, at the time the menstruation suddenly ceased, that she noticed the sudden increase in her hands. Her face at this time also underwent changes, … so that when the patient returned home none of her relatives could recognize her…. The whole feet are large, including the toes. Though the latter are increased in size, they have preserved their form, there is no true deformity, their appearance is simply that of a very big person…. The tongue is enlarged. The patient is a little deaf, and the sight is also slightly defective…. The cranial vertex is of nearly the same size as the end of the chin. The lower jaw is well developed…29

In addition to a detailed description of this patient’s acromegalic appearance, Marie also reported a finding consistent with diabetes insipidus: “The patient’s thirst is intense, obliging her to beg tea of her friends in order to satisfy it. The quantity of urine is excessive.…”29

The second case was that of a 54-year-old woman who developed amenorrhea at the age of 29 years. The year after that, the patient completely lost her vision and became permanently blind. This patient went on to notice incremental increases in the size of her head, hands, and feet. Marie described:

The borders of the orbits are very thick, also the frontal eminences, making between them and the upper border of the malar bone a deep depression, something similar to the corresponding region of a cow. The nose is large. The lower jaw is very thick….29

In addition to coining the term “acromegaly,” Marie’s major contribution to the field was the establishment of a unique clinical entity, whose characteristics he vividly described with his detailed case reports. Although he did not postulate on the underlying pathophysiological mechanisms of acromegaly, he did state that he believed the disease was not attributed to previously implicated origins, such as myxedema or Paget disease. Marie’s work was followed by a thesis on acromegaly by his intern, Souza-Leite, who further bolstered these arguments with more case reports (Fig. 2).38 At this point in time, the cause of acromegaly was still not known. However, it is interesting to note that Marie frequently observed the occurrence of great hypertrophy of the pituitary body.38

Pituitary Tumors and Sellar Enlargement: an Observation in Patients With Acromegaly

The underlying pathophysiological mechanism of acromegaly and gigantism was an area of great debate since the time of Saucerotte in 1801.36 Verga,45 in 1864, reported sellar enlargement in a patient with acromegaly. After that, multiple reports emerged suggesting the connection between acromegaly and pituitary pathological entities. In 1887, Oscar Minkowski33 of Germany published a series of autopsy studies that strengthened this association. He found pituitary enlargement in all patients with acromegaly, and was probably the first to realize the causal relationship between acromegaly and pituitary enlargement. Massalongo30,31 attributed acromegaly to pituitary hyperfunction by demonstrating pituitary tumor cells that contained granular cytoplasm in a patient with acromegaly. In 1898, Woods Hutchinson22 described the association between pituitary hyperfunction and clinical acromegaly. Despite the multiple observations of pituitary tumors in patients with acromegaly, the link between the two remained controversial for many years.

The relationship of acromegaly and gigantism was also an area of contention. Marie28,29 and Souza-Leite38 believed that these were distinct entities. As detailed in Bartels’ account,3 Fritsche and Klebs, on the other hand,
believed that acromegaly and gigantism were the same disorder, the former being acquired and the latter congenital. Evidence for a pituitary cause of gigantism was supported by Hutchinson’s pathological descriptions of a French giantess known as Lady Aama (Fig. 3). She died at the age of 18 years and stood 6 feet, 7.75 in tall. Pathological examination of her skull revealed a very large pituitary fossa (31 × 37 mm) and a huge frontal sinus. Hutchinson’s stated: “The pituitary body was found to be greatly enlarged…. It appeared to be about the size of a pigeon’s egg…” It was eventually recognized that both acromegaly and gigantism had the same underlying pathogenesis, but differed in the patient’s age at onset. Acromegaly occurred in adulthood (Fig. 4), whereas gigantism occurred in childhood prior to the closure of the growth plates in the long bones (Figs. 5 and 6).

*Harvey Cushing: Postulation of Pituitary Hyperfunction*

The debate about an underlying pituitary disorder in acromegaly continued in the early 1900s. Harvey Cushing, in his book *The Pituitary Body and Its Disorders: Clinical Status Produced by Disorders of the Hypophysis Cerebri*, further tackled the debate by describing the 4 prevailing theories of the pituitary origin of acromegaly and gigantism. The first theory was postulated by Marie, who stated that the clinical manifestations were due to pituitary hyposecretion. The second theory, advocated by Massalongo, Tamburini, Benda, Modena, and Fisher, proposed that pituitary hypersecretion was the cause. In the third theory,
clinical acromegalic features were attributed to a nutritional disorder, with the pituitary enlargement as a secondary manifestation. This theory was supported by Gauthier, Strumpell, Vassale, and Guerrini. The fourth theory, proposed by Silvestrini, Arnold, Warda, and Petren, suggested that there was no causative relationship between clinical acromegaly and the pituitary gland.

Cushing supported the theory of pituitary hypersecretion (Fig. 7) and stated:

Certainly most of the circumstantial evidence in our possession points in the direction of an oversecretion, whether normal or pathological; and this is at least the most acceptable present working hypothesis.

Cushing was so certain of a pituitary source of acromegaly that in 1909 he obtained permission to open the skull of the Irish Giant, Charles Byrne (also known as O'Brien) of Littlebridge, Ireland (Fig. 8). Mr. Byrne, who was thought to be the tallest person with acromegaly of his time, stood 7 feet, 7 in tall, and died in 1783. His body was promptly acquired by Dr. John Hunter, who boiled all the flesh off the bones and ultimately put the skeleton on display, without having performed any anatomical dissection. When Cushing opened the skull, he found an enlarged pituitary fossa measuring 21 × 24 × 11 mm, suggestive of glandular hypertrophy. Cushing’s theory of pituitary hypersecretion was also supported by his own observations of clinical remission in patients with acromegaly who underwent hypophysectomy. In 1909, he was among the first to postulate a “hormone of growth” in the pituitary gland, which laid the foundation for the hypothesis that hyperfunctioning of the anterior pituitary was responsible for the manifestations of acromegaly.

Fig. 5. Preadolescent hyperpituitarism with giant overgrowth in a patient who was referred to Dr. Cushing in 1910 (from Cushing’s The Pituitary Body and Its Disorders: Clinical Status Produced by Disorders of the Hypophysis Cerebri).

Fig. 6. Photograph of a 3-year-old patient with a hypophyseal tumor, exhibiting gigantism and adiposity (from Cushing’s The Pituitary Body and Its Disorders).
The Establishment of a Hormone of Growth: Birth of Neuroendocrinology

The development of the recognition of acromegaly and gigantism as clinical entities cannot be concluded without an understanding of the endocrinology system as it relates to the pathogenesis. In 1902, following an elegant set of experiments on dog intestine, Bayliss and Starling demonstrated that an extract of duodenal mucosa injected into the bloodstream resulted in stimulation of pancreatic secretion, and named this active material “secretin.” They proposed a hormone system in which substances produced at one site had the ability to bring about physiological changes at a distant site without a direct neural stimulus. The term “hormone” (from the Greek meaning to excite) was introduced by Starling at the suggestion of William Hardy in 1905. Although Cushing was the first to postulate a pituitary “hormone of growth” in 1912, it was not until 1944 when growth hormone was finally isolated by Li and Evans, as detailed by Kaplan. Furthermore, it was not until the 1950s that the insulin-like growth factors were discovered by Salmon and Daughaday, as described by Van den Brande. The measurement of endocrine function would later be revolutionized by radioimmunoassays. The physiological mechanisms of the growth hormone and insulin-like growth factor system were eventually understood. Innovations in modern neuroimaging, pituitary surgery, radiotherapy, and medical therapy contributed to the advancements that set the stage for modern medical and surgical management of acromegaly and gigantism.

Conclusions

Although accounts have appeared in the lay literature for millennia, the recognition of acromegaly and gigantism as clinical pathological entities has evolved over the last 125 years. The cornerstone was laid by Marie, with his establishment of acromegaly as a distinct clinical phenomenon. Following this, a multitude of anatomical, pathological, and physiological studies have added to our clinical understanding, with pituitary hypersecretion of growth hormone being established as the underlying pathophysiological mechanism. As we establish new techniques for the management of this fascinating disease, the clinical evolution of acromegaly and gigantism continues to be of tremendous interest.

Disclosure

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