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Review

GIGANTISM AND ACROMEGALY THROUGH HISTORY

Maša Malenica[1], Tena Trbojević[1], Stjepan Herceg[1], Monika Kukuruzović[1], Iva Šeparović[1], Nina Rotim[2] and Krešimir Rotim[3]

[1]Division of Pediatric Neurology, Department of Pediatrics, Sestre milosrdnice University Hospital Center, EpiCARE center, Zagreb, Croatia;

[2]student, School of Medicine, University of Zagreb, Zagreb, Croatia;

[3]Department of Neurosurgery, Sestre milosrdnice University Hospital Center, Zagreb, Croatia

SUMMARY – Giants and acromegalists have long captured attention, and they were often almost mythical creatures of great strength and power. Due to their expressive appearance, they were recorded in myths and works of art much earlier than they were of interest to medical practitioners. The first recognition was made by a Dutch physician Johannes Wier in 1567, but the first description and appellation originated by Pierre Marie in 1886. Involvement and interest from neurosurgeons followed, and in 1907, Hermann Schloffer performed the first transsphenoidal surgery in a patient with pituitary adenoma. In 1909, Harvey Cushing linked removal of the enlarged pituitary gland to regression of acromegaly and considered 'growth hormone' a pathophysiological trigger. Knowledge of acromegaly has been enhanced by the discovery of growth hormone (GH) and insulin-like growth factor (IGF-I) and evidence for an association between GH hypersecretion and elevated circulating IGF-I with the clinical phenotype. After 1970, pharmacotherapy (dopamine agonists, somatostatin analogs and GH receptor blockers) was introduced. Despite advances in drug therapy and radiotherapy, surgical treatment still provides optimal results (first-line treatment) after more than a century of attempts. In this paper, we present gigantism and acromegaly over time, important turning points from its recognition to the current insights and fundamental approach reminding us of the immense prosperity of medicine and science. The development of basic sciences and clinical endocrinology will enable progress and improvement of comprehension in the pathogenesis and diagnostics, as well as curative modalities.

Key words: *Acromegaly; Gigantism; Growth hormone; History; Pituitary gland; Pituitary tumors*

Introduction

Acromegaly and gigantism are rare clinical entities caused by hypersecretion of growth hormone (GH) produced by solid monoclonal somatotropic pituitary adenoma that occurs sporadically[1]. Sometimes, due to inheritance, mutations of different genes in germline cells occur familiarly or are associated with other conditions and syndromes[2]. Extremely rarely, gigantism and acromegaly result from the production of insulin-like growth factor (IGF-I) from another neoplasm. Gigantism and acromegaly captured attention of people due to their grotesque appearance and great stature as giants. In history, they were often described as mythical creatures of great strength and power[3]. With their pronounced expressive appearance, they were recorded in myths and works of art much earlier than

Correspondence to: *Prof. Maša Malenica, MD, PhD*, Division of Pediatric Neurology, Department of Pediatrics, Sestre milosrdnice University Hospital Center, Vinogradska c. 29, HR-10000 Zagreb, Croatia
E-mail: masa.malenica@kbcsm.hr, malenicamasa96@gmail.com

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they were of interest to medical practitioners. Despite numerous discoveries from the first descriptions of mechanisms and treatment, over the past two decades, studies related to acromegaly have continued to rise[4-7]. In this paper, we present gigantism over time, i.e., important turning points from recognition to future insights that occur sometimes nearly simultaneously or with astonishing order in those difficult times, all reminding us of the immense prosperity of medicine and science, as well as the tight connection of surgical and non-surgical fields.

Methods

In this narrative brief work, we included analysis of articles available through the PubMed database, Google Scholar and other prominent literature, including medical internet web pages and bases. Considering the historical perspective of the main topic, we did not use the exclusion criterion of the year when the cited article was published. We also searched the list of references for articles to find potential publications that we may have missed in the search.

Historical perspective as clinical entities

Mythologies of various religions, ethnic groups or geographical regions are often rich in bizarre beings. For example, in the Bible, Goliath of Gath was a giant three feet tall, as were his father and three brothers, and he fought on the side of the Philistines until the boy David hit him with a slingshot in the forehead and mortally wounded him[5-7]. Legends and myths in the past, just like this biblical one, often reveal a characteristic weakness typical of acromegalists despite their imposing physical appearance. Since people were fascinated with their physical appearance, artists often immortalized their acromegalic changes in different types of art. In Ancient Egypt, the artist made a stone figure of the pharaoh Akhenaten of the eighteenth dynasty of Amarna who had typical acromegalic characteristics[8]. Besides art, one of the other methods to determine the occurrence of gigantism and acromegaly is osteoarcheological research. Although the findings of acromegaly in archeology are rare and sometimes dubious, the diagnosis of this disease can be confirmed by certain bones[8,9].

Even though acromegalic changes were frequent in history, ancient physicians could not explain the cause. Despite their enviable knowledge and skills, they often misinterpreted pituitary function. The first of them was Hippocrates, who believed that the brain was a gland that secreted cold juices that cooled the body from warming caused by the work of the heart[10]. Furthermore, Claudius Galen, known for numerous experiments and autopsies, believed that fluid was created in the brain, which was then transported to the pituitary gland and the base of the brain, following the lamina cribrosa and nose as waste material, saliva[11]. During the Renaissance, there was rapid progress in science, art and medicine when scientists (e.g., Paracelsus, Leonardo da Vinci, Andreas Vesalius, Fallopius Gabriello, Bartolomeo Eustachi) made numerous anatomical studies involving the head and brain area, whereas the pituitary gland was named *glandular pituitam cerebri excipiens* with the function of secreting mucus from the nose[12,13]. After Galileo Galilei discovered a telescope and microscope in 1609, an insight into the structure of the glands was enabled. Prussian king Frederick William (17th century) gathered a unit of tall soldiers called the Potsdam Giants whose leader was two meters and ten centimeters tall, and none of the soldiers was shorter than 180 cm. The giants became the bodyguards of kings and nobility, such as Staffordshire's blacksmith with gigantic stature, Walter Parsons. In the 18th century, a Scottish surgeon named John Hunter performed numerous experiments and contributed to the endocrinology, as well as by displaying the skeleton of the famous Irish giant Charles Byrne in the Hunter Museum[12]. Along with scientists describing giants in their research, in many countries across Europe, it was common to show giants at various exhibitions and fairs. During the 19th and first half of the 20th century, the embalmed bodies or skeletons of some giants became exhibits in some museums, most notably the Barnum's American Museum in New York, which opened in 1842[14].

First medical descriptions of acromegaly and gigantism

Medical descriptions of this disease came quite late. Due to rare occurrence and the fact that its pathophysiology required knowledge of endocrinological mechanisms, most of the early research gradually took place during the first half of the 20th century, as noted in Table 1[15-22]. The first professional detailed description of acromegaly was published by a Danish physician and ophthalmologist Johannes Wier in 1567, when he described a young girl of gigantic habitus who traveled with her mother

to fairs, where she was shown as a sensation. The patient's parents were of average height, but after the age of 14, she gradually lost her period and began to grow rapidly to gigantic proportions[15]. Gradually, during the 18th and 19th centuries, other descriptions of cases followed. The Italian neuropsychiatrist Andrea Verga met a patient whose face was pale and deformed by acromegalic changes, which he called prosopectasiae. When she died of typhus in 1864, a walnut-sized sellar tumor that dislocated the optic nerve without the presence of normal pituitary tissue was found on autopsy[16]. A few years later, the term 'macrosomia' was used by the Italian physician and criminologist Cesare Lombroso[19]. In 1877, the French physician Henri Henrot published an autopsy report of a patient with a sellar tumor and mistook acromegaly for myxedema, calling the enlargement of the bowel organ splanchnonzegalía[17]. In the same year, Vincenzo Brigidi, an Italian physician described autopsy results of the Italian actor Ghirlenzoni with typical acromegalic habitus and, by using microscopic examination for the first time, revealed a pituitary tumor in an enlarged pituitary gland[19]. One of the most important and earliest case descriptions of the pathological-anatomical appearance of pituitary tumors with all characteristic changes in the body was given in 1884 by Fritzsche and a pathologist Klebs[23]. Although case reports of this disease were becoming more common, acromegaly as a separate entity was not present in the reality of medicine and physicians[19]. However, in 1886, Pierre Marie, a French neurologist, described in detail clinical presentation of two cases, distinguishing this disease as a separate entity. While using the Greek words άκρος (*acros*, edge, limb) and μεγάλος (*megalos*, large), he named this clinical entity 'acromegaly'. At the time, Marie and his collaborator Souza-Liete interpreted pituitary enlargement as part of the general enlargement of all organs[18,24]. They believed that acromegaly and gigantism were two completely different diseases; in particular, gigantism was considered an excessive variant of normal development, and acromegaly a pathological condition. Several authors in the following years shared this opinion, until 1887, when Oscar Minkowsky, a Lithuanian endocrinologist-diabetologist, was the first to report that pituitary enlargement was found in all postmortem studies of patients with acromegaly, thus leading to a causal relationship between pituitary enlargement and acromegaly[25]. The pathophysiological mechanisms of acromegaly and gigantism were still the subject of numerous discussions at the end of the 19th century.

Initiative of clinical and pathogenetic associations

In 1895, Edouard Brissaud, a French physician and pathologist, and Henry Meige, a French neurologist, described a case of the acromegalic giant Mazas, 230 cm tall, known as the giant from Monastruc. This description was the first indication that acromegaly and gigantism shared the same pathogenetic mechanism but different periods of inception[26]. Then, in 1898, during autopsy of a French giant woman known as Lady Aama, Hutchinson found a large pituitary fossa filled with tumors. Only a few years later, Carl Benda, a German pathophysiologist, associated acromegaly with eosinophilic pituitary tumors and thus confirmed the assumptions of his predecessors[19]. From a series of published articles, it gradually became clear that both diseases had the same pathogenetic mechanism but differed with respect to the age at onset. Gigantism will appear much earlier in life, when the skeleton still has growth potential, i.e., in the prepubertal period[27]. Four fundamental theories of acromegaly and gigantism were noted and cited by Harvey Williams Cushing, the father of modern neurosurgery. As follows, the first theory was advocated by Marie, who believed that the clinical manifestations of acromegaly occurred due to pituitary hypofunction. The second theory was advocated by Massalongo, according to whom acromegaly was caused by hypersecretion of the pituitary gland. The third theory was originated by Gauthier, who related clinical acromegalic properties to nutritional disorders, while pituitary enlargement was a secondary consequence. The fourth theory was advocated by Silvestrini and his like-minded people, who considered no causal connection between acromegaly and the pituitary gland[20]. In 1909, Cushing introduced the concepts of 'hyperpituitarism' and 'hypopituitarism' and explained gigantism and acromegaly by overstimulating growth[21]. Overproduction of pituitary GH as the cause of acromegaly and gigantism became clear in the early years of the 20th century[28]. Cushing was among the first to postulate GH in the pituitary gland, confirming the fact that anterior pituitary lobe hyperfunction was responsible for the expression of acromegaly[29]. At the peak of his neurosurgical career, Cushing realized that the underlying pathological process in acromegaly occurred at the molecular level, not in morphological structures[30].

Table 1. Documented and notable first clinical descriptions of gigantism and acromegaly[15-22]

Name of physician and specialization	Life span	Work description
Johannes Wier, physician and ophthalmologist	1511-1588	First professional detailed description of acromegaly (young girl of gigantic habitus who traveled with her mother to fairs where she was shown as sensation)
Nicolas Saucerotte, surgeon	1741-1841	Published report of a 39-year-old man with right clinical description corresponding to acromegaly
Jean-Louis-Marc Alibert, dermatologist	1768-1837	Description of acromegalic changes
Andrea Verga, neuropsychiatrist	1811-1895	Description of a patient whose face was pale and deformed by acromegalic changes, later autopsy discovered a walnut-sized sellar tumor
Henri Henrot, physician	1838-1919	Published autopsy report of a patient with sellar tumor and mistook acromegaly for myxedema
Pierre Marie, neurologist	1853-1940	Detailed description of clinical picture of two cases of disease – using the term acromegaly as a separate clinical entity
Oscar Minkowsky, endocrinologist	1858-1931	First report of pituitary enlargement in postmortem studies of patients with acromegaly

Discovery and role of growth hormone

Cushing's description of GH from 1912 could not be proven until it was isolated in 1944 by Herbert McLean Evans. Unlike Cushing, Herbert McLean Evans, Professor of Anatomy and Embryology at the University of Berkeley, used experimental methods and in 1944 provided convincing evidence for the biological endocrine effects of pituitary extract[22,31,32]. In collaboration with Choh Hao Li, an American chemist of Chinese descent, Evans managed to isolate several pituitary hormones, including GH and determined its structure, which was a major step forward in diagnosis[33]. In 1948, Kinsell *et al*. found an increased concentration of GH in the blood of patients with acromegaly[34]. Almost simultaneously, the British neuroscientist Geoffrey Wingfield Harris, an anatomist at the University of Oxford, laid the foundations of modern neuroendocrinology after studying portal blood flow to the pituitary gland and the interaction of the brain and endocrine organs[35]. In 1968, Ladislav Krulich, a Czech-American scientist, in collaboration with Samuel M. McCann, an American scientist, discovered a hypothalamic factor that inhibited GH secretion, which was later called somatostatin[28]. On the other hand, William Doughaday, an American endocrinologist, and his co-workers discovered a substance induced by GH that mediated the effects of GH on peripheral tissues and named it somatomedin C which was later recognized as the same as IGF-I[36-38].

Treatment options

Pituitary surgery: salvaging but delicate and challenging approach

After anatomical studies, Hermann Schloffer, an Austrian surgeon, noticed in 1907 that the nasal cavity and the sphenoid bone sinus reached the front wall of the pituitary fossa, which enabled him to successfully reach the central part of the skull base and the pituitary fossa, and operate pituitary tumors by a new transsphenoidal approach with the least operative trauma[39]. Soon after, pituitary transsphenoidal surgery developed independently as a useful method around the world, even being practiced by Harvey Cushing[40]. In first third of the 20th century, Jules Hardy, a Canadian neurosurgeon, as one of the pioneers, 'returned' this method and improved the transsphenoidal approach by introducing an operating microscope and intraoperative x-ray control, achieving selective adenoma removal while preserving healthy pituitary tissue[41]. Very few methods in medicine are still relevant after 100 years. A century after the introduction of the transsphenoidal approach, over 95% of tumors in the sellar region are operated on by this method[42]. However, pituitary (transsphenoidal) surgery requires an experienced pituitary surgeon and is technically challenging, with steep learning curves and differences in the performance of individual surgeries leading to variable surgical outcomes among centers[43]. Tertiary multidisciplinary centers of excellence were therefore developed around the world with a large series of operated patients whose results improved clinical practice. Pediatric patients represent even more demanding operative settings. Due to the rarity, complexity and diversity from adult cases, recommendations regarding optimal management of pediatric pituitary adenoma are debated, with attention given to growth and development changes, as well as fertility[44]. Historically, in our country, pituitary surgery transferred from otorhinolaryngology field into the domain of neurosurgery gradually in the second half of the 20th century, and it was nourished afterwards in our tertiary center[41].

Radiological visualization

From the first x-rays of enlarged sella turcica in a patient with acromegaly taken in 1899 by Hermann Oppenheim, one of the German leading neurologists, modern methods have come a long way[45]. Particular progress has been shown later by the introduction of computed tomography (CT). Due to its superior contrast resolution and multiplanar representation of soft tissue structures, magnetic resonance imaging (MRI) of the sellar and parasellar regions is nowadays the gold standard in visualization (and diagnosis) before the transsphenoidal approach[46-48].

Radiation therapy: introduction of additional treatment options for controlling the disease

After laying the foundation for surgical accessibility, which at that time was followed by perioperative morbidity and mortality, there were other therapeutic attempts for pituitary tumors besides surgery. Immediately after the discovery of x-rays, radiotherapy for pituitary tumors was introduced. The first application was described in 1909 by Antoine Beclere, a French radiotherapist[49]. In 1968, Lars Leksell, a Swedish neurosurgeon, introduced the gamma knife

prototype into neurosurgery[50]. With the development of CT and MRI, technological conditions for pituitary radiosurgery have been created[51,52]. Traditional radiosurgery (gamma knife) enables treatment of smaller pituitary adenomas, whereas for remaining large invasive adenomas out of range due to size or location, a robotic radiosurgery CyberKnife system based on a 3D image and computer controls allows the treatment of such tumors with high-energy rays from several different directions[53,54]. Nevertheless, radiotherapy is usually reserved as third-line therapy for patients with persistently high levels of GH despite surgery and pharmacotherapy[55].

Expansion of medication treatment

In the early 1970s, the dopamine agonists bromocriptine and cabergoline were recognized as potentially effective agents in the treatment of hyperprolactinemia and acromegaly[56]. The discovery of mediators between GH and target tissue IGF-I allowed clinicians to assess treatment options more accurately[57]. Medicaments such as somatostatin receptor ligand (SRL, octreotide for example), dopamine agonist (cabergoline) and growth hormone receptor antagonist (pegvisomant) are used individually, or in combination in cases of resistant and recurrent tumors[58-60]. Combined therapy (SRL + pegvisomant) showed normalization of IGF-I in more than 90% of patients[61]. New protocols of medicament therapy emerged and are reserved for patients with persistently high levels of GH after surgery or, primarily, for patients who cannot undergo surgery[60-62]. In addition, the imminent application of gene therapy could be expected, whereas experimental research with adenovirus vectors is ongoing[63].

Conclusions from Experiences Leading to Expectations in the Future

The path to diagnosis and, consequently, appropriate and successful management of acromegaly remains challenging. Observation of historical experiences is instructive and fascinating. Despite all the improvements in surgery techniques, numerous controversies and doubts have remained since the time of Cushing. The development of molecular biological techniques has provided better insight into the pathogenesis and paved the way for the future application of nanomedicine, gene therapy, and ultimately fully personalized medicine in the treatment of acromegaly. At the same time, the digital era offers new technology and robotic assistance, which improves and revolutionizes the neurosurgery approach. Advances in the recognition and evolution of basic sciences and clinical endocrinology will enable further progress in understanding the pathogenesis and diagnosis, thus, remarkably increasing the treatment options and prognosis of patients with acromegaly and gigantism.

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Sažetak

GIGANTIZAM I AKROMEGALIJA KROZ POVIJEST

M. Malenica, T. Trbojević, S. Herceg, M. Kukuruzović, I. Šeparović, N. Rotim i *K. Rotim*

Giganti i akromegaličari svojim osebujnim izgledom i stasom od davnina su zaokupljali pozornost ljudi te su često prikazivani mitskim bićima velike snage i moći. Od najranije povijesti zbog ekspresivnog izgleda zabilježeni su u mitovima i umjetničkim djelima znatno ranije negoli su zainteresirali medicinske praktičare. Prvi pokušaj medicinskog opisa dao je nizozemski liječnik Johannes Wier 1567. godine. Međutim, Pierre Marie 1886. godine detaljno opisuje kliničku sliku i prvi put upotrebljava termin "akromegalija". Zanimanje neurokirurga rezultiralo je izvođenjem operativnog zahvata u bolesnika s adenomom hipofize prvi put transfenoidnim pristupom u 1907. (Hermann Schloffer). Godine 1909. Harvey Cushing povezuje odstranjivanje povećane hipofize i regresiju akromegalije, a „hormon rasta" smatra patofiziološkim okidačem. Spoznaje o akromegaliji unaprijeđene su otkrićem hormona rasta (GH) i inzulinu sličnog faktora rasta (IGF-I) te dokazom povezanosti hipersekrecije GH i povišenim cirkulirajućim IGF-I s kliničkom slikom. Nakon 1970. godine uvedene su medikamentne mogućnosti poput agonista dopamina, analoga somatostatina i blokatora GH receptora. U ovom radu prikazujemo gigantizam kroz vrijeme, od prepoznavanja do današnjih spoznaja, podsjećajući nas na neizmjerni doseg medicine i znanosti. Razvoj bazičnih znanosti i kliničke endokrinologije omogućuje napredak u razumijevanju patogeneze i dijagnostike, kao i kurativnih terapijskih modaliteta.

Ključne riječi: *Akromegalija; Gigantizam; Hipofiza; Hormon rasta; Povijest; Tumori hipofize*