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The Surgical Management of Acromegaly

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Abstract

Acromegaly is the condition produced by one of the benign tumors of the pituitary gland. These tumors produce a variety of disorders affecting many parts of the body, producing side effects related to abnormal hormone function. The dramatic appearance of the acromegalic giant has attracted attention over the ages. This chapter summarizes the history of the recognition and ultimate diagnosis of acromegaly. The biological and physiological elements are described. The methods of diagnosis and management are elaborated. Although the focus of the chapter is on the surgical approach for treatment, alternative strategies are also discussed, along with the outcomes of management for patients and the restoration of quality of life as a primary goal.

Keywords: acromegaly, gigantism, growth hormone, pituitary surgery, endoscopic surgery

1. Introduction

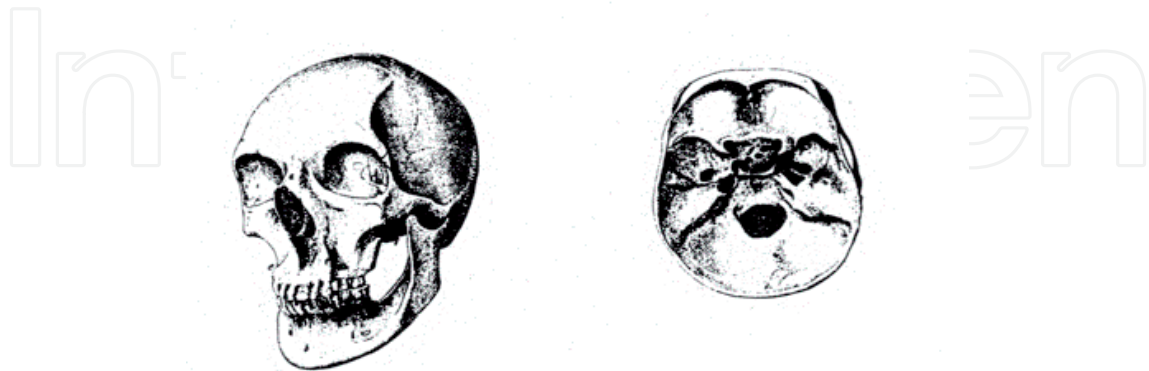
By 1800, the existence of human “giants” had been established through legends and stories for centuries. Up to that point, the story of “O’Brien the Irish Giant” was one of the most intriguing. Charles Byrne, O’Brien’s given name, was born in Ireland in 1761 and died in London in 1783 at the age of 22 [1]. During the course of his short life, his legend grew to the level of national fame in Great Britain and continued after he died. Byrne’s notoriety stemmed from his terrific stature, alleged at the time to be 8 feet 4 inches. In truth, he stood at about 7 feet and 7 inches tall, still towering over the spectators who paid to see him. As a teenager, Byrne left Ireland for Britain, where he intended to make a name for himself by displaying his body and charging people for the chance to come see him. Sadly, Byrne’s career would end tragically one night at a pub where he was robbed of his life’s earnings, as much as £700. He died shortly

thereafter. Upon his death, a competition began among medical professionals to secure the rights to his corpse, in some cases for the purpose of scientific research, in others out of curiosity and greed. Byrne had foreseen this outcome and had made it known that he did not wish for anyone to dissect his body after he died, requesting that he be buried at sea [1]. This did not stop the pursuit of Byrne's body, and it was the infamous John Hunter who "managed to surreptitiously procure Byrne's corpse from a dishonest person among Byrne's companions for a large sum, quoted at £500." [1] Instead of examining Byrne's pituitary fossa, Hunter was actually seeking Byrne's body as a collector's item and decided to display the man's skeleton in his museum [2]. For over a century, his skull would remain unexamined; in the meantime, the medical world's understanding of gigantism and acromegaly would grow exponentially.

In 1864, the Italian neurologist Andre Verga first documented a patient who displayed symptoms of a certain affliction which he named "prosopectasia," or a widening of the face, a common sign of the disease we now call acromegaly [3] (**Figure 1**).

That same year, Verga also became one of the earliest investigators to report an acromegalic subject with a finding of sellar enlargement, growth of the area of the skull that contains the pituitary gland. The major event in the timeline of scientific research was Pierre Marie's creation of the diagnostic term "acromegaly" in 1886 [3]. This marked the first time that the characteristics and symptoms of the condition were succinctly summarized and published, although works before Marie's had mentioned many of the same symptoms in patients displaying gigantism [3]. In the years after Marie's paper, investigators began to understand that tumors of the pituitary caused glandular enlargement and were the root of the disease, dispelling previously held notions that they were simply by-products of gigantism. The debate still raged about the relationship between acromegaly and gigantism. At first, Marie believed acromegaly to be pathological, while gigantism was simply an extreme of normal human development. It became apparent after inspecting famous giants' skeletons that the disorders had a "pathogenetic mechanism, but differed with regard to the age of onset." The consensus

PROSOPECTASIA



Verga A : Caso singolare di prosopectasia. Reale Istituto Lombardo di Scienze e Lettere, Classe Scienze Matematiche e Naturali 1864.

Figure 1. Verga's description of prosopectasia (Author's collection).

was that gigantism has an earlier onset than acromegaly, appearing while the individual is still growing, but that acromegaly occurs after puberty when the person had completed normal growth [3].

The first decade of the 1900s brought concentrated emphasis on the underlying pathological causes behind acromegaly, expanding on the identification of the pituitary as the affected area. This research became part of the basis for the entire “hormone theory.” In 1902, E.H. Starling and W.M. Bayliss conducted an experiment in which they injected duodenal extract into a dog intestine, causing the pancreas to become activated and to secrete what was later termed “secretin.” [4] Three years later, with the advice of William Hardy, Starling became the first to use the term “hormone” to describe this phenomenon “in which substances produced at one site had the ability to bring about physiological changes at a distant site without a direct neural stimulus.” [4] At this point, four major theories of the pituitary’s relationship to gigantism and acromegaly had emerged. The first, most notably supported by Marie himself, was that pituitary hyposecretion was the cause. Rebuking this notion, distinguished members of the field, including Massalongo, Tamburini, Benda, Modena, and Fisher, believed that acromegaly was due to pituitary hypersecretion [4]. A third theory, supported by Gauthier, Strumpell, Vassale, and Guerrini, was that it was merely the result of a nutritional disorder and that oversized pituitary fossae were by-products of the disease. Finally, a fourth camp maintained that there was no causation whatsoever between the pituitary and acromegaly.

No one was more influential with his or her work on the pituitary than Dr. Harvey Cushing, author of *The Pituitary Body and Its Disorders*, published in 1912 [4]. Cushing was a proponent of the second theory that an overactive pituitary led to acromegaly and gigantism. The detail in his case studies was second to none, and with his meticulous research, he was able to compile a comprehensive analysis of the disease’s true nature. In fact, Cushing became the first person to open the skull of the original Irish Giant, Charles Byrne, in 1909, over a century after Byrne’s death. Still held in Hunter’s collection, Byrne’s worst fears became a reality when Cushing examined his skull to find that he had, as many had long since assumed, an unnaturally large pituitary fossa. In addition to this momentous discovery, Cushing also described a large number of acromegalic patients in his 1912 book (**Figure 2**).

With the image above, Cushing detailed one of the more striking aspects of the disease, the physiological changes to which the affected body is subjected. This instance in particular, which was the first to be mentioned in his long list of case studies, shows a man who would have been described as simply a “normal giant” before the onset of the disease [5]. By this, Cushing meant that while he was an outlier in terms of height before he was afflicted, and this was due to natural growth that did not have anything to do with an enlargement of the pituitary. It was also at this time that, building upon Starling and Bayliss’s work on hormones, Cushing became the first to posit that the pituitary was responsible for secreting a “hormone of growth,” a massive step toward what would prove to be the correct understanding of gigantism and acromegaly. The way in which modern medicine understands and treats acromegaly and gigantism would not have been possible without each person, professional, and patient, mentioned in this book, as well as countless others who go unmentioned, who are all owed a great deal of gratitude for their contributions.



Figure 2. One of Cushing's acromegaly patients from 1910, "M. Van W.," the picture on the left shows the subject pre-acromegaly at age 25. The middle and right pictures show the same man just 10 years later at 35, with obvious acromegalic changes [4].

2. Making the diagnosis

For most patients, acromegaly is a subtle and slowly progressive illness. The clinical findings evolve so slowly that it is often 5–10 years or more before patients seek medical attention. The primary symptoms and signs of acromegaly are listed in **Table 1**. They include progressive enlargement of facial features, hands, and feet; enlargement of the jaw with spacing of the teeth and malocclusion of bite; increased perspiration, with oily skin and a tendency to have acne and skin tags; joint pains; low-back pain; and headache [6].

There are a number of comorbidities characteristic of acromegaly [7]. They include elevated blood pressure, diabetes mellitus, obstructive sleep apnea (OSA), snoring, enlargement of the tongue and upper airway structures, hyperlipidemia, and, in some cases, cardiomyopathy. They are listed in **Table 2**.

A variety of laboratory testing abnormalities can occur in patients with acromegaly. The cardinal features are elevation of serum growth hormone (GH) and IGF-1. Elevations in these hormones are present in patients with active acromegaly, and they are essential for making the diagnosis. Some patients may have elevations in prolactin as well. Pressure on the normal pituitary gland from the tumor can produce a decrease in cortisol, thyroid hormones, and testosterone levels, and abnormalities of gonadotropin hormones can produce fertility problems in women.

Because the location of the pituitary tumor that produces acromegaly is at the base of the skull in the area called the sella turcica, imaging diagnosis is routinely done by magnetic resonance imaging (MRI). Occasionally other imaging studies are helpful in making the diagnosis and in planning treatment. These include computerized tomography (CT) scans to accurately evaluate bony structures, angiography to delineate the vascular elements around the area of the tumor, and rarely nuclear imaging studies such as PET scans [7, 8]. A typical pituitary tumor (macroadenoma) producing acromegaly is seen in **Figure 3**.

Excessive growth: height, hands, feet, hat size, facial features (brow, nose, lips, tongue, jaw), joints (arthropathies), acral bones

Oily skin, acne, excessive sweating (hyperhidrosis), skin tags

Dental gapping, malocclusion

Headache, chest pain

Carpal tunnel syndrome

Table 1. Symptoms and signs of acromegaly.

Hypertension, cardiomyopathy

Diabetes mellitus

Obstructive sleep apnea

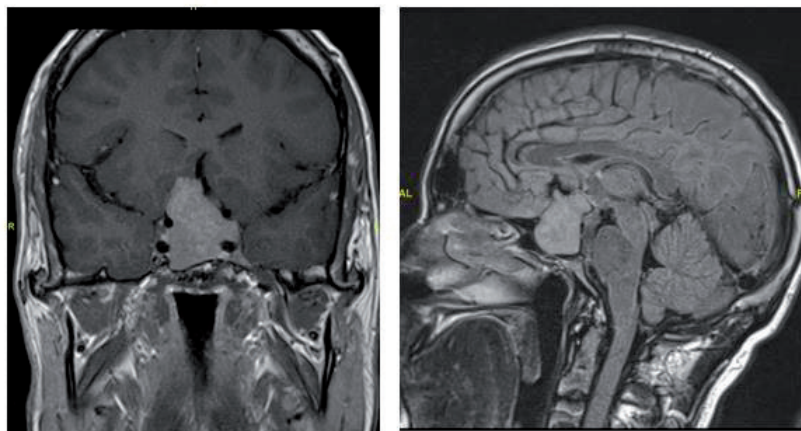
Hyperlipidemia

Visual loss (from tumor growth)

Colonic polyps

Table 2. Comorbidities of acromegaly.

Imaging



Coronal and Saggital images of a GH secreting Macroadenoma

Figure 3. MRI images of a large invasive GH macroadenoma.

3. Classification of growth hormone-secreting tumors in acromegaly

There are two basic characterizations of the size of pituitary tumors. Microadenomas are tumors that are less than 10 mm in maximum diameter. Macroadenomas are those tumors 10 mm or more in maximum diameter. There is also a characterization of uncommon “giant” adenomas that are defined as being 3 or 4 cm in maximum diameter. A further classification

is related to tumor cell invasion of the structures around the pituitary. These include invasion of the dural membranes surrounding the pituitary and invasion of the cavernous sinuses on either side of the pituitary (Knosp grading) [9]. Tumors that extend above the pituitary into the suprasellar space can come in contact with the optic chiasm and produce progressive visual loss. The size and stage of these tumors help determine both the goals of surgery and the outcomes for the patients. Occasionally, a pituitary tumor may develop what is called pituitary tumor apoplexy [10] wherein there is hemorrhage into the tumor with rapid enlargement, sometimes involving an emergency situation requiring prompt surgery and prompt cortisol replacement.

4. Indications for surgical management

For the majority of patients, the presence of active acromegaly alone is the indication for surgery, in those patients well enough to undergo anesthesia and the surgical procedure. In addition to halting the relentless progress of acromegaly, successful surgical removal is considered to be “first-line” management [11] and often can also correct visual loss and ameliorate intractable and life-threatening comorbidities. Adjunctive and second-line therapies include various forms of radiation therapy and a number of pharmacologic approaches that are helpful when surgery is either contraindicated or becomes ineffective. Ultimately, the goal is improving the quality of life of our patients with acromegaly.

5. Preoperative evaluation and preparation

In patients being considered for general anesthesia and surgery, a careful preoperative evaluation must be performed [12, 13]. This includes obtaining a full panel of pituitary-focused laboratory testing, with repletion of any hormones that may be deficient, particularly cortisol and thyroid hormone. Repletion of thyroid deficiency must be handled very slowly, as the associated increase in metabolic rate may require adding supplementary cortisol to cover the stress of surgery. It is also important to note that the serum chemistries are in the normal range, especially sodium, potassium, and calcium.

Patients with significant hypertension need to be controlled, and those with a risk of cardiomyopathy must be fully evaluated by a cardiologist. Those patients with diabetes mellitus will need to be managed throughout the surgery and hospitalization to maintain satisfactory glucose levels. Patients with symptomatic obstructive sleep apnea may require particular attention with regard to airway management during surgery and in the postoperative period. It is desirable to alert the anesthesia team in advance for patients who have acromegaly. Acromegaly patients often have difficult airways and may require awake fiber-optic intubation. If the imaging studies show that there is a more than the usual risk of damage to blood vessels in the region of the pituitary, particularly the carotid arteries, an arterial line may be a useful adjunct during anesthesia and postoperatively when and if intensive care

unit observation might be necessary. Management of intraoperative fluids and postoperative intake and output of fluids is a critical part of the recovery process for the patients, many of whom will require a urinary catheter during the operative and the postoperative periods.

In some cases of large, invasive, suprasellar GH-secreting tumors, preoperative medical therapy can be useful in shrinking the size of the tumor, making it smaller and safer to remove surgically (**Figure 4**).

The patient is a 32-year-old aviator. After the onset of loss of libido 8 years prior to surgery, he noted the progressive onset of evolving symptoms, including increased shoe and hat size,

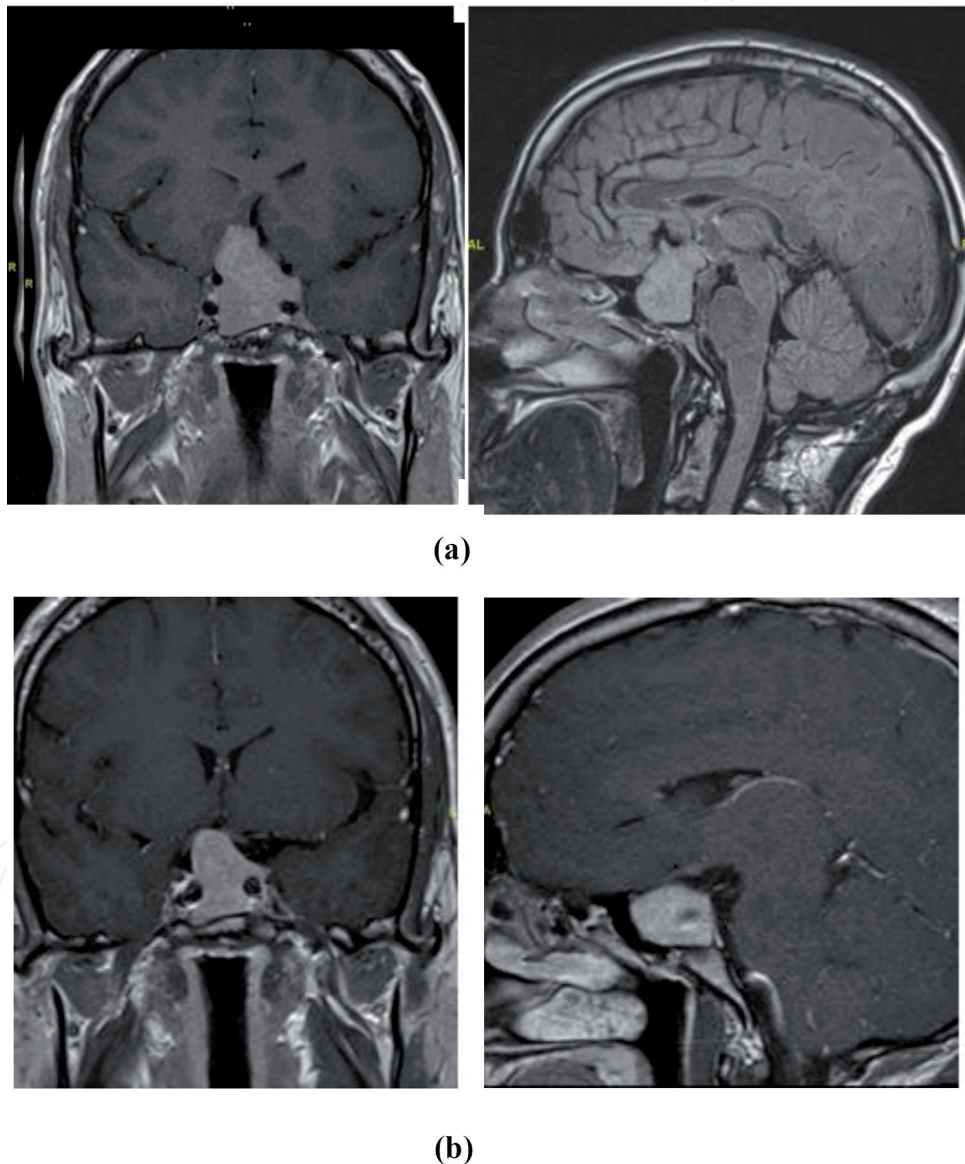


Figure 4. Case illustration. (a) Pre-treatment coronal and sagittal images of invasive GH macroadenoma as seen in **Figure 3**. (b) Post-treatment coronal and sagittal images after 3 months of Lanreotide producing major shrinkage, facilitating the subsequent operation (See Section 9). Postoperatively he had normalization of Growth Hormone and IGF-1, and is back flying airplanes!

jaw enlargement, frontal bossing, skin tags, decreased muscle mass, hyperhidrosis, and loss of energy and increasing fatigue. Visual examination revealed 20/20 acuity, bitemporal visual field loss, and decreased retinal fiber layer on ocular computerized tomography. Laboratory investigation revealed low testosterone, FSH, and LH, slightly elevated prolactin at 21.3, low cortisol at 3.6, and elevated growth hormone and IGF-1 at 3.3 and 632, respectively. After 3 months of treatment with lanreotide (Somatostatin analog), the tumor decreased in size and became more amenable to thorough surgical removal.

6. Surgery: methods and considerations

There are two basic routes of access for surgery on patients with acromegaly. Currently, the most utilized is a transnasal transsphenoidal approach using either the operating endoscope or the operating microscope for visualization [8, 14]. Large tumors that extend into the intracranial space and involve the brain, optic chiasm, and major blood vessels are often treated with a craniotomy, so that intracranial structures in danger can be fully visualized in a safe fashion. Because the access to the pituitary is through the nose and the sphenoid sinus, it is often helpful to have the assistance of a qualified otorhinolaryngologist to assist with problems such as nasal septal deviations, septal spurs, imperfect pneumatization of the sphenoid sinus, and other obstacles that may appear during the approach [15]. Patients with acromegaly often have unusually stout bony structures and robust nasal and sinus mucosa which can account for significant bleeding if not carefully controlled. Once the sella turcica has been opened, the dura of the pituitary is incised, and the pituitary tumor is encountered. Every effort is made to spare normal pituitary gland and to accomplish a thorough removal of the growth hormone-secreting pituitary adenoma. Occasionally the tumors are invasive of the dura and adjacent structures. Removal of these portions can increase the risks of surgery but may be essential for developing a complete remission of acromegaly. Some tumors perforate the diaphragm of the sella and after their removal can result in an intraoperative spinal fluid leak. These leaks must be controlled to avoid meningitis. A practical method is to utilize fat taken from the abdomen to fill the empty space left by removing the tumor and secure this leak in an effective fashion [8]. The area of leakage through the sella can also be reinforced with a carefully constructed nasal septal flap [15]. This strategy for repair has been highly effective in preventing postoperative spinal fluid leakage and meningitis. The duration of surgery is usually less than 3 hours, and patients awaken promptly after recovering from anesthesia.

7. Pathology of pituitary tumors in acromegaly

Tumor specimens from surgery are analyzed with great care. Using immunocytochemical techniques, most of the tumors can be fully characterized [16]. The majority express growth hormone only. Because the tumors that produce acromegaly and elevated prolactin secretion come from the same cell line, a number of them are characterized as growth hormone-prolactin

staining where some of the tumor cells will stain for one and/or the other of those two hormones. Another less common variant is the mammosomatotroph tumor where each tumor cell can express both growth hormone and prolactin. There is also an acidophil stem cell tumor that is a primitive variant of the latter. The hormone staining is related to the granules within the tumor cell cytoplasm, and they can be classified as either densely granulated or sparsely granulated, with some evidence that the sparsely granulated tumor cells are more aggressive. These tumors producing acromegaly, including the plurihormonal variant, are derived from a cell lineage expressing the Pit-1 transcription promoter. Additionally, the mitotic index is evaluated and the proliferation index of the tumor cells is characterized by MIB-1 staining. These studies are very helpful in correlation with the clinical course of the patients postoperatively.

8. Potential risks and complications of surgery

In experienced hands, the potential risk of serious complications and adverse events is less than 2%. There are, however, potential problems that must be considered and measures taken for prevention of complications [8].

There is a risk of infection, including meningitis, and this may be associated with a spinal fluid leak that ultimately will need repair. Vascular complications can occur and include injury to the carotid arteries, other sources of bleeding from peripheral arteries, veins, and mucous membranes. These can result in vasospasm, stroke, and postoperative epistaxis. Problems with fluid balance can occur, particularly if the posterior pituitary gland or the infundibulum is injured during the operation. This can result in diabetes insipidus which must be carefully treated until it resolves or is corrected by medication with DDAVP. Another issue with regard to fluid balance is the syndrome of inappropriate secretion of ADH (SIADH) which can result in symptomatic hyponatremia which must be carefully and slowly corrected in order to avoid serious problems [17].

9. Medical management of acromegaly

Careful studies of the biology and pathology of growth hormone-secreting pituitary tumors in acromegaly have led to a number of medical strategies for assisting in the treatment of this disorder [5, 11, 13, 18]. The tumor cells that produce increased amounts of growth hormone and prolactin are derived from the same cell lineage. For that reason, a dopamine agonist which is used to treat hyperprolactinemia is moderately effective in helping to control acromegaly. The most commonly used dopamine agonist preparation is cabergoline, usually given by mouth twice a week, and it is usually well-tolerated. Another class of medical agents consists of somatostatin analogs such as octreotide or lanreotide [5]. They have greater effectiveness than cabergoline and also have the possibility of shrinking the size of some growth hormone-secreting pituitary tumors. They are effective in approximately 60% of patients. Another class

of drug to treat acromegaly is pegvisomant [18], a growth hormone receptor antagonist. It is given by injection, usually on a daily basis, and is exceedingly expensive at this time. It can be used in combination with somatostatin analogs, improving on the individual results of the two drugs. None of these medical therapies is completely free of side effects.

10. Adjunctive radiation therapy

Another second-line therapy is the use of radiation, which can be delivered in a variety of different timing schedules and with variations in the radiation physics in a number of different modalities that are currently in use [19, 20]. Conventional fractionated teletherapy has been used for some time but currently is being supplanted by more focused methodologies termed stereotactic radiosurgery. The radiosurgical methods include the Gamma Knife, CyberKnife, linear accelerator with multileaf collimator, the proton beam, and the carbon ion beam. Some of these can be given by “single shots” or by fractionation. Each of the modalities has its advantages and disadvantages. With modern techniques, the risks of damage to surrounding neural structures, including the optic nerves and chiasm, and delayed appearance of radiation-induced neoplasms are quite low. In patients with acromegaly, there is a fairly long delay time for the radiation to gradually lower the growth hormone and IGF-1. Most of the techniques currently utilized are effective but are also associated with a significant degree of radiation-induced hypopituitarism regarding the other hormones.

11. Criteria for remission after therapy

Clinical signs of remission of acromegaly tend to occur fairly early in those patients who have a satisfactory result of treatment. Some clinical signs improve rapidly, especially difficulty with the upper airway and snoring, along with the diminishment of excessive perspiration, and gradual improvements in the soft tissue issues affecting the hands, feet, and facial features. Headache is often alleviated. Arthropathies tend to linger much longer, but ultimately improve in many patients. Some patients with hypertension and diabetes will manifest progressive clinical improvement, which gradually occurs over time. More than 80% of patients who have visual compromise are improved postoperatively.

Biochemical remission is critical, and normalization of the serum levels of growth hormone and IGF-1 is monitored to assess the pace and degree of remission [11, 14, 15]. It often takes 3 months or more for IGF-1 to reach its nadir after surgery, but the growth hormone response occurs more promptly. Additionally, the dynamics of growth hormone regulation can be measured by performing an oral glucose tolerance test and measuring the response of growth hormone, which should become significantly decreased after a glucose challenge.

Ordinarily, we wait 3 months to obtain a definitive postoperative MRI scan which will serve as a baseline for the future. For the initial few years, annual MRI studies are often recommended, and they are done if there is not a complete remission or if there is a recurrence of

symptoms and/or abnormal laboratory results. We recommend that the pituitary hormones and IGF-1 be measured every 6 months for the first several years.

12. Outcomes of surgical management of acromegaly

Initial remission of acromegaly as measured by clinical and biochemical criteria occurs in 50–60% of macroadenomas and 80–90% of microadenomas [11, 13, 21]. Results are less effective when the surgeon is dealing with large macroadenomas or tumors that are invasive of surrounding structures. Postoperative improvement in the management of diabetes mellitus and hypertension is seen in approximately 75% of patients. The majority of patients who present with obstructive sleep apnea develop improvement after successful surgery. Although pituitary adenomas are generally benign tumors that do not progress to malignancy, tumor recurrence does develop in some patients over time. After initial successful surgery, recurrence will develop in approximately 8% of patients within the first 10 years following successful surgery. Because the objective of all forms of management of acromegaly are to improve the quality of life of the patient, a number of questionnaires and instruments have been developed [21, 22] to measure quality of life, and they provide good insight as to the results of current therapy and for areas with needs for improvement. Studies have demonstrated that sustained remission of patients with acromegaly provides mortality figures similar to the general age-matched population [23]. There is evidence to suggest that significant surgical experience is a major factor in achieving optimal outcomes [23]. Although great strides have occurred, continuous development of knowledge concerning the genetics and molecular biology of acromegaly will undoubtedly provide us with more versatile and effective avenues of progress.

13. Conclusion

Acromegaly is the current quintessential example of a hyperfunctioning tumor of the pituitary gland. It is usually a benign tumor; however, it has multiple side effects and comorbidities that threaten the life and wellbeing of the patient. Steady progress has been made since its original description in understanding the pathophysiology of pituitary adenomas. We have learned a great deal about the molecular biology and hypothalamic regulation of pituitary cells that secrete growth hormone and induce elevations in IGF-1. At present, the first-line therapy is surgery to remove the tumor, usually by the endonasal transsphenoidal approach, often with the aid of a surgical endoscope. The results of surgical management are generally excellent, and techniques and outcomes are steadily improving. Initial criteria for the development of centers of excellence for pituitary adenoma diagnosis and treatment are being developed [24]. Surely, further scientific investigation will improve the nonsurgical adjunctive management of growth hormone-secreting pituitary tumors, primarily using appropriate drugs that target the physiological and genetic mechanisms of these tumors that secrete excess growth hormone.

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References

- [1] Muinzer TL. A grave situation: An examination of the legal issues raised by the life and death of Charles Byrne, the 'Irish Giant'. *International Journal of Cultural Property*. 2013;**20**(1):26
- [2] Mammis A, Eloy JA, Liu JK. Early descriptions of acromegaly and gigantism and their historical evolution as clinical entities. *Neurosurgical Focus*. 2010;**29**(4):1
- [3] Herder WW. Acromegaly and gigantism in the medical literature. Case descriptions in the era before and the early years after the initial publication of Pierre Marie (1886). *Pituitary*. 2009;**12**(3):236
- [4] Cushing H. *The Pituitary Body and Its Disorders*. London: J.B. Lippincott; 1912. p. 30
- [5] Colao A, Grasso L, Giustina Q, Melmed S, Chanson P, Pereira A, et al. Acromegaly. *Nature Reviews Disease Primers*. 2019;**5**:20
- [6] Iuliano SI, Laws ER. Recognizing the clinical manifestations of acromegaly: Case studies. *Journal of the American Association of Nurse Practitioners*. 2013;**26**(3):136
- [7] Powlson AS, Gurnell M. Cardiovascular disease and sleep-disordered breathing in acromegaly. *Neuroendocrinology*. 2016;**103**:75-85
- [8] Laws ER Jr, Cote DJ, Iuliano S. Transsphenoidal surgery for acromegaly. In: Laws ER Jr, editor. *Transsphenoidal Surgery*. New York: Springer International; 2017. DOI: 10.1007/978-3-319-56691-7_25
- [9] Knosp E, Steiner E, Kitz K, Matula C. Pituitary adenomas with invasion of the cavernous sinus space: A magnetic resonance imaging classification compared with surgical findings. *Neurosurgery*. 1993;**33**:610-617
- [10] Semple PL, Jane JA Jr, Lopes MB, Laws ER. Pituitary apoplexy: Correlation between magnetic resonance imaging and histopathological results. *Journal of Neurosurgery*. 2008;**108**:909-915
- [11] Katznelson L, Laws ER, Melmed S, Molitch ME, Murad MH, Utz A, et al. Acromegaly: An endocrine society clinical practice guideline. *The Journal of Clinical Endocrinology and Metabolism*. 2014;**99**(11):3933-3951

- [12] Melmed S, Colao A, Barkan A, Molitch M, Grossman AB, Kleinberg D, et al. Acromegaly Consensus Group. Guidelines for acromegaly management: An update. *The Journal of Clinical Endocrinology and Metabolism*. 2009;**94**:1509-1517
- [13] Nachtigall L, Delgado A, Swearingen B, Lee H, Zerikly R, Klibanski A. Extensive clinical experience: Changing patterns in diagnosis and therapy of acromegaly over two decades. *The Journal of Clinical Endocrinology and Metabolism*. 2008;**93**:2035-2041
- [14] Kreutzer J, Vance M, Lopes M, Laws ER Jr. Surgical management of GH-secreting pituitary adenomas: An outcome study using modern remission criteria. *The Journal of Clinical Endocrinology and Metabolism*. 2001;**86**:4072-4077
- [15] Jane JA, Starke RM, Elzoghby MA, Reames DL, Payne SC, Thorner MO, et al. Endoscopic transsphenoidal surgery for acromegaly: Remission using modern criteria, complications, and predictors of outcome. *The Journal of Clinical Endocrinology and Metabolism*. 2011;**96**(9):2732-2740
- [16] Zada G, Cavallo LM, Esposito F, Fernandez-Jimenez JC, Tasiou A, De Angelis M, et al. Endoscopic transsphenoidal surgery in patients with longstanding acromegaly: Operative strategies for overcoming technically challenging anatomical variations. *Neurosurgical Focus*. 2010;**29**(4)
- [17] Laws ER, Lopes MB. The new WHO classification of pituitary adenomas: Highlights and areas of controversy. *Acta Neuropathologica*. 2006;**111**:80-81
- [18] Buchfelder M, van der Lely AJ, Biller B, et al. Long-term treatment with pegvisomant: From observations from 2090 patients in ACROSTUDY. *European Journal of Endocrinology*. 2018;**179**:419-427
- [19] Ding D, Mehta GU, Patibandla MR, et al. Stereotactic radiosurgery for acromegaly: An international multicenter retrospective cohort study. *Neurosurgery*. 2019;**84**:717-725
- [20] Jagannathan J, Sheehan JP, Pouratian N, Laws ER, Steiner L, Vance ML. Gamma knife radiosurgery for acromegaly: Outcomes after failed transsphenoidal surgery. *Neurosurgery*. 2008;**62**(6):1262-1269
- [21] van der Lely A, Gomez R, Pleil A, et al. Development of ACRODAT, a new software medical device to assess disease activity in patients with acromegaly. *Pituitary*. 2017;**20**(22):692-701
- [22] Giustina A, Bronstein M, et al. Staging and managing patients with acromegaly in clinical practice: Baseline data from the SAGIT validation study. *Pituitary*. 2019;**22**:476-487
- [23] Swearingen B, Barker F, Katznelson L, Biller B, Grinspoon S, Klibanski A, et al. Long term mortality after transsphenoidal surgery and adjunctive therapy for acromegaly. *The Journal of Clinical Endocrinology and Metabolism*. 1998;**83**:3419-3426
- [24] Casaneuva F, Barkan A, Buchfelder M, et al. Criteria for the definition of pituitary tumor centers of excellence (PTCOE): A pituitary society statement. *Pituitary*. 2017:489-498

