

Total Hypophysectomy could be Cost-Effective and Associated with a Better Prognosis in the Management of Acromegaly in Low Resourced Settings: Observation of a Case Series

Martine Claude Etoa Etoga^{1,2*}, Anne Boli Ongmeb², Figuim Bello^{3,4}, Mesmin Dehayem^{2,5}, Jean Claude Mbanya^{2,5}, Vincent de Paul Djientcheu^{4,6} and Eugène Sobngwi^{2,5}

Abstract

Acromegaly is associated with enhanced cardiovascular mortality. This implies that its treatment must be complete and effective. The consensus for the management of acromegaly has a well-codified protocol. The normalization of IGF-1 and a low GH value are essential for healing. The management of acromegaly is cumbersome. Many African countries do not have the proper technical platform to manage this condition. Radiotherapy centres are non-existent in some regions and somatostatin analogues, when available, are inaccessible because of their high cost. Thus, the prognosis of acromegaly seems reserved in underprivileged areas. In this series of 6 patients followed for acromegaly, total hypophysectomy appeared to bring a better prognosis compared to standard treatment. This would suggest that in the absence of an optimal technical platform, total hypophysectomy should be considered in the treatment of acromegaly in less developed countries.

Keywords: Hypophysectomy; Acromegaly; Radiotherapy; Somatostatin analogues; Macroadenomas

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Introduction

Acromegaly is a rare condition [1]. In 90% of cases, it is linked to Growth Hormone (GH) hypersecretion by a somatotrophic pituitary adenoma. Very rarely, GH hypersecretion may be related to ectopic stimulation by hypothalamic GHRH or carcinoid syndrome (bronchial tumor) [2]. Owing to its insidious nature, diagnosis is always delayed (4 to 10 years or more) [3]. When the diagnosis is made, the clinical presentation is always evocative of an unsightly and characteristic dysmorphic facial syndrome. The increase in the size of the fingers and feet is very evocative. The diagnosis is confirmed on assays with high IGF-1 levels adjusted to age and associated increase in GH concentration not suppressed during an Oral Glucose Tolerance Test (OGTT).

Acromegaly is associated with excess mortality of cardiovascular origin in the majority of cases, followed by respiratory causes and neoplasia. Thus, in absence of treatment, the survival of these patients would be reduced by 10 years [1,4]. In view of this data, effective and complete treatment of acromegaly is recommended. According to the consensus of acromegaly management established by the French Endocrine Society, the first-line treatment is surgery with complete excision of the tumor when the latter is removable and the patient surgically-fit. After this, the possibility of associating a medical treatment or radiotherapy

by gamma-knife can be discussed. With this algorithm, complete healing is achieved solely by surgical treatment in 30-50% of cases if it is a macroadenoma and 80%-90% with a microadenoma. However, success of therapy will depend on tumor size and the neurosurgeon's experience [5,6]. In addition to this, radiotherapy, which is a complementary treatment, is associated in over 80% of cases with the occurrence of anterior pituitary insufficiency of

¹Department of Clinical Sciences, University of Douala, Douala, Cameroon

²Endocrinology and Metabolic Diseases Unit, Yaoundé Central Hospital, Yaounde, Cameroon

³Neurosurgery Unit, Yaoundé Central Hospital, Yaounde, Cameroon

⁴Department of Surgery and Specialties, University of Yaounde, Yaounde, Cameroon

⁵Department of Internal Medicine and Specialties, University of Yaounde, Yaounde, Cameroon

⁶Neurosurgery Unit, Yaounde General Hospital, Yaounde, Cameroon

*Corresponding author:

Martine Claude Etoa Etoga, Department of Clinical Sciences, University of Douala, Douala, Cameroon

Tel: 237677481756

✉ claudetoga@yahoo.fr

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varying severity. This can affect the quality of life of patients, not to mention the risk of damage to the surrounding organs. Cases of optic neuritis have been reported. Increasingly, medical therapy seems to supplant radiation therapy. This includes somatostatin analogues or GH receptor antagonists. In addition, this treatment is not devoid of side effects. Indeed, there are risks of vesicular lithiasis and steatorrhea observed at treatment onset. The success rate with somatostatin analogues is about 60% to 85% of cases regarding the decline or normalization of GH. Whereas, a reduction of the tumor occurs in 30% to 50% of cases [7,8]. Again, there is a compressive tumor risk with macroadenomas. GH receptor antagonists lower 90% of the hormone parameters, but the treatment is very expensive [9].

Finally, the complete treatment of acromegaly remains difficult with an almost inconsistent cure. In some sub-Saharan African countries such as Cameroon, there are gaps in the technical platform for optimal management of patients suffering from acromegaly. The prognosis of acromegaly in sub-Saharan Africa is poor [10]. The overall accessibility to health care, but above all, the unavailability and high cost of somatostatin analogue and pegvisomant, make difficult the optimal management of acromegaly. Especially when it is known that these drugs need to be imported into the country and their intake requires regular hormonal monitoring. Another impediment is their suppressive effect of hormonal secretion hence the duration of treatment remains indefinite to this day. There is no radiotherapy centre in Cameroon. Total hypophysectomy as well as radiation therapy will be associated with anterior hypopituitarism. However, a simple supplementation of the vital axes (corticotrophic and thyreotropic) would ensure better survival of patients at a lower cost if done properly. We report the cases of 6 patients followed in endocrinology, all for acromegaly secondary to a somatotrophic macroadenoma and treated according to the standard algorithm predetermined by the Endocrine Society; and of which one underwent a total hypophysectomy with a different outcome.

Case Presentation

Case report 1

Miss M was a 32-year-old Cameroonian black woman. She was admitted in the medical emergency ward in December 2015 for Hyperosmolar Non Ketotic State (HONK) with glycemia raised at 33 mmol/l. It was the discovery of diabetes. She had a medical history of macrosomia and gestational diabetes without follow-up after delivery. On clinical evaluation we were struck by the highly evocative dysmorphic syndrome of acromegaly. She already had complete blindness in the left eye and temporal hemianopsia in the right eye. Given the diagnosis of diabetes, we measured GH levels which returned above normal (GH>150 mUI/l) and IGF1 at 866 ng/ml (Normal range: 87-278 ng/ml). Other pituitary workup showed hypogonadism and hypothyroidism. Cerebral CT Scan diagnosed a pituitary macroadenoma measuring 32 × 40 × 17 mm. After stabilization of glycemia, the patient was operated. Complete resection of the tumor was not possible since there was invasion of cavernous sinus. A month after surgery, IGF-1 dropped but remained high at 586.3 ng/ml. Therefore, we completed the treatment with cabergoline owing to the absence of somatostatin analogue in our local context and limited financial resources. The

patient died 5 months after surgery in a context of HONK.

Case report 2

A 65-year-old black woman of Cameroonian nationality with a 10-year history of high blood pressure presented to our hospital in November 2016 with persistent pain of the fingers and wrists. She was previously treated in neurosurgery for bilateral carpal tunnel syndrome. She complained about increase of size of feet and fingers. She reported that her family noticed modification of her face. A large pituitary tumor measuring 10 × 17 × 22 mm was diagnosed by MRI. There was suprasellar extension without compression of the optic chiasma and invasion of the left cavernous sinus.

Acromegaly was confirmed by standard endocrinological workup. Her GH level was >40 ng/ml and was not suppressed by a standard oral glucose load. Her IGF-1 level was 651 ng/ml (Normal range: 41-241 ng/ml).

Surgery was first discussed, but she refused, and we started lanreotide 60 mg as initial dose. After 4 weeks there was no significant reduction of IGF1-1. It was 535 ng/ml, so we increased to lanreotide to 120 mg. Due to unavailability of lanreotide, the patient treatment was discontinuous. Finally, after 10 months, we were informed of her death at home by her family members. The presumed cause of death was cardiovascular disease.

Case report 3

Mr B. a 60 years old Cameroonian black man. He went to consultation in February 2015 for chronic headaches and visual disturbances. He also complained of wrist pain later diagnosed as carpal tunnel syndrome. A diagnosis of macroadenoma was made on pituitary MRI showing a lesion involving the pituitary gland measuring 15 × 16 × 21 mm. There was invasion of the medial wall of the right cavernous sinus. The tumor extended unto the optic chiasm and raised it. Hormonal workup confirmed acromegaly with IGF1: 532 ng/ml (Normal range: 48-241 ng/ml) and unsuppressed GH on OGTT. First-line treatment was surgery with partial resection of the tumor by transsphenoidal approach. MRI 1 year after surgery showed that there was a 4 mm × 10 mm remaining tissue on axial plane that extended to the right cavernous sinus wall without invasion. There was no gross residual tumor on MRI. Laboratory tests showed that GH remained unsuppressed and IGF1 level was high. We therefore discussed for gamma-knife radiotherapy in a specialized center overseas. The patient was admitted at a hospital in Paris (France) where he received gamma-knife radiotherapy in 2018. Laboratory workup done in 2019 showed a residual secretion of GH at 1.4 mUI/ml after OGTT. In March 2019 the patient had a cardiac arrest at home and died.

Case report 4

Mr D.S is a 44-year-old black Cameroonian. He presented at consultation for screening of diabetes in January 2018. While examining him, we realized that he had an acromegaly facies, and he declared an increase of the size of his feet and fingers. He also had a decreased vision on the sides. Hormonal workup showed: GH: 107 mUI/l; IGF-1: 592 ng/ml (Normal range: 75-249 ng/ml). Cerebral CT scan diagnosed a macroadenoma of 12 × 17

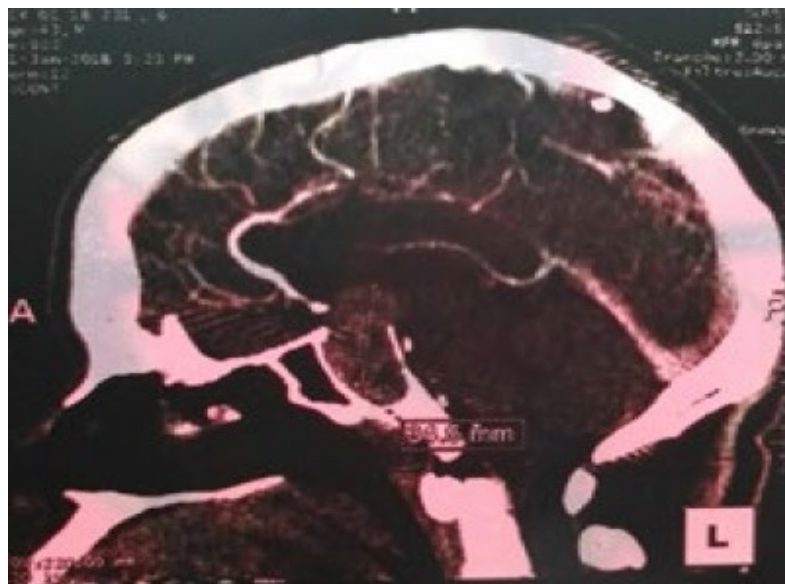


Figure 1: Sagittal view of cerebral CT scan showing a pituitary macroadenoma.

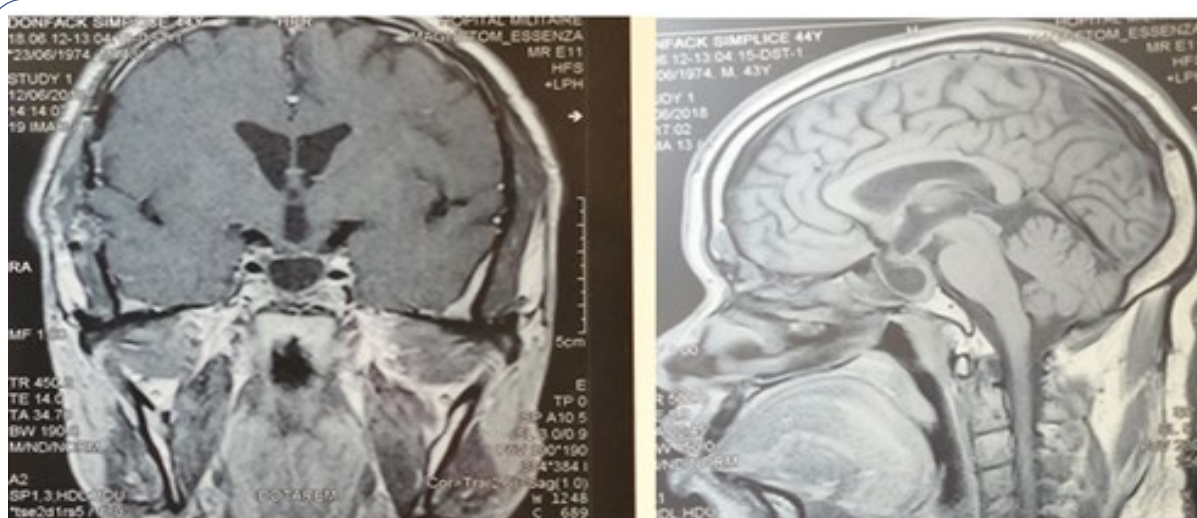


Figure 2: Post-surgery MRI showing total hypophysectomy.

× 34.5 mm (**Figure 1**). After multidisciplinary discussion involving endocrinologists and neurosurgeons, a total hypophysectomy was chosen as therapeutic option for this patient. Thus, the patient underwent total hypophysectomy in February 2018. He was substituted with hydrocortisone, levothyroxine, and testosterone enanthate and minirin to prevent panhypopituitarism. Three months after surgery IGF-1 was 69 ng/ml; 8 a.m cortisol 77 ng/ml; free T4: 7.4 ng/ml. Post-surgery MRI showed an empty sella with no residual tumor (**Figure 2**). During the 1st and 2nd years after surgery; the patient complained of erectile dysfunction and early morning asthenia when he didn't take his medication. IGF1 remained low and stable at 65 ng/l and 59 ng/ml respectively during these controls. We continued hormonal substitution of deficient axes except the somatotrophic axis. The patient is no longer on ADH substitution.

Case report 5

Mrs M, a 43-year-old black woman was referred to the endocrinology unit for the management of a macroadenoma. She started to complain of wrist pains and chronic headaches in the last 2 years; associated to the increased of the size of fingers and feet. Clinical examination of the showed bitemporal hemianopsia. A pituitary MRI was directly performed revealing a macroadenoma of 33 × 17 × 20 mm with a repression of the optic chiasm and invasion of the right cavernous sinus and sheathing of the right intracavernous carotid. At the admission in the endocrinology unit we were struck by the evocative dysmorphic syndrome of acromegaly. Hormonal work up showed elevated IGF1: 352 ng/ml (Normal range:75-249 ng/ml) there was no evidence of hypopituitarism. Patient travelled to Belgium

Table 1: Evolution of IGF-1 during treatment in the overall patient series.

IGF-1	Diagnosis	1 month	3-4 months	1 year	2 years
Patient 1	IGF1: 866 ng/ml		IGF1:586 ng/ml	-	-
Patient 2	IGF1:651 ng/ml	IGF1:535 ng/ml	-	-	-
Patient 3	IGF1: 532 ng/ml	IGF1:306 ng/ml	-	IGF1:245 ng/ml	IGF1:252 ng/ml
Patient 4	IGF1:592 ng/ml	-	IGF1:69 ng/ml	IGF1:62 ng/ml	IGF1:59 ng/ml
Patient 5	IGF1: 352 ng/ml	IGF1: 299 ng/ml	IGF-1:283 ng.ml	-	-
Patient 6	IGF1:304.7 ng/ml	-	-	-	-

Table 2: Estimated cost of treatment of acromegaly after surgery: Standard compared to total hypophysectomy.

Treatment	Standard (monthly cost in €)	Total hypophysectomy (monthly cost €)
Somatostatine analogue	1100-1600 €	0 €
Pegvisomant	2400-5000 €	0 €
Levothyroxine 100 µg	0 €	5.80 €
Hydrocortisone	0 €	2.40 €
Testosterone enanthate	0 €	8.18 €

where she underwent surgery which was not complete because of invasion of the right cavernous sinus and intracavernous carotid. 1 month after surgery IGF-1 dropped to 299 ng/ml and she started lanréotide. She come back to Cameroon while waiting for a rendez-vous for radiosurgery in Belgium. Because of the unavailability of somatostatin's analogue, she was advised to take cabergolin. IGF-1 on cabergoline remains stable at 283 ng/ml. The patient retained wrist pain and carpal canal syndrome. She is waiting for another medical evacuation for the continuation of her treatment.

Case report 6

A 51-year-old black Cameroonian woman came to our consultation in August 2019 for the management of a pituitary macroadenoma operated in 2007. The macroadenoma was diagnosed in 2007, revealed mainly by visual disturbances associated to headaches. She had been operated in a hospital in Paris. The macroadenoma was initially classified as nonfunctional pituitary macroadenoma. She received no hormonal treatment, and she came back to Cameroon. In 2019 she started to feel pain in her fingers, reported increase in size of her hands and feet. Her shoe size increased from 40 to 42. Hormonal workup showed: IGF-1: 304.7 ng/ml (Normal range: 55-234 ng/ml). GH after OGTT was not suppressed. GH T0: 1.9 mUI/l went to 1.5 mUI/l after 1 hour. There was no evidence of pituitary deficiency. MRI was performed revealing a macroadenoma of 20 × 19 × 13 mm with suprasella extension, compression of the optic chiasm and invasion of the right cavernous sinus. We concluded to a

recurrence of a secreting somatotrophic macroadenoma and we discussed about a total hypophysectomy for this patient.

Results and Discussion

This series of 6 cases describes the evolution of patients during the treatment of acromegaly. In general, the prognosis remains poor: 3/6 patients died; 1 patient remains with residual IGF-1 secretion and a carpal tunnel syndrome and 1 presented a recurrence of a secreting somatotrophic macroadenoma responsible of an acromegaly. Only one patient at this stage of follow-up over 2 years could be declared cured. As in many series, the diagnosis of acromegaly was made late [10,11]. The acromegaly dysmorphic syndrome was very evocative and the etiology for all was an invasive pituitary macroadenoma.

The majority of patients underwent surgery. Only complete resection of the tumor guarantees healing. Treatment has not been optimal in the majority of our patients because somatostatin analogues are not marketed in Cameroon. Some patients were able to import them, but the cost of the product did not allow regular treatment, and at some point, the patient interrupted treatment. An alternative with cabergoline which has an antitumoral effect in addition to its antisecretory use has been considered and suggested in the literature [12]. Unfortunately, the results are often unsatisfactory as shown by the first case. Radiation therapy when available completes surgical treatment in case of residual secretion [7]. Our patient number 3 had been able to benefit from gamma-knife radiosurgery in Europe. While it is true that gamma-knife provides a cure in 48%-53% of cases

for residual hypersecretion, its effects are only visible over time (7 to 10 years) (13). Patient 3 nevertheless retained a residual secretion of GH and IGF-1 during the year of gamma-knife realization and unfortunately died of cardiac arrest the same year. In this case, there was also this discontinuous intake of lanreotide which prevent the normalization of IGF-1 and GH while awaiting the effect of radiosurgery. In the end, although there was an attempt of tumor resection, it was incomplete due to proximity to the cavernous sinuses. This is an important parameter to consider for the chances of recovery. When surgery was done, it was conducted by the same neurosurgeon, who has over 20 years of experience. Studies show that even in the absence of a macroscopically visible tumor, GH hypersecretion and therefore IGF-1 is associated with excess mortality in acromegaly [5,11]. Hence the healing criteria is set at a normal value of IGF1 and suppressed GH < 1 µg/l (14). It is well known that the treatment of acromegaly is very onerous. Each step of the treatment: surgery, drug and radiotherapy should be cost-analyzed for the decision making-process. Cost-effectiveness studies on treatment of acromegaly suggest that economic models should be developed following health economics guidelines recommendations [13-15].

The trial of a total hypophysectomy treatment for acromegaly was decided in a multidisciplinary team to achieve these objectives, driven by the high mortality which is mainly related to the unavailability of optimal and complete treatment in our context. The risk would be the occurrence of a 100% anterior hypopituitarism as will be the case with radiotherapy. Notwithstanding, correct supplementation would ensure a better prognosis. In addition, hormonal substitution is available and accessible in Cameroon. Patient 4 underwent a total hypophysectomy and saw his IGF-1 and GH levels drop significantly throughout his follow-up. **Table 1** shows the evolution IGF-1 of all patients in the serie. Patient 4 is properly supplemented and is now adapted to his new lifestyle. Since the dysmorphic signs are not reversible, he retained bone deformities. Estimated monthly cost of the treatment is around 1100-1600€ for a patient who underwent surgery completed by somatostatin analogues. And it could be higher if used pegvisomant [11]. For a patient based in sub-Saharan region, we should consider additional cost including travel fees and substantial means. In patient 4, the monthly cost was 16.38€ with a declared healing after 2 years of follow-up. **Table 2** compares different costs of the treatment after surgery in case of standard treatment versus total hypophysectomy.

One limitation in the follow-up of our patients is the lack of regular simultaneous IGF-1 and GH assays, and the lack of post-operative MRI in some of our patients. The adaptation in monitoring required us to refrain from requesting regular blood tests as patient care was costly and none of these patients had social security. Indeed, the social security system is not yet operational in Cameroon.

Conclusion

Although there are competent human resources, the management of acromegaly is still difficult to implement in Cameroon due to

the lack of a technical platform. Total hypophysectomy in this context appears to be associated with a better prognosis at the expense of properly substituted anterior pituitary insufficiency. Total hypophysectomy could therefore be a first-line alternative in acromegaly patients, when the socio-economic context is unfavorable..

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