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"Acromegaly In Focus: Experience Of The Endocrinology And Diabetology Department, CHU Hassan II, Fes"

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Abstract
Acromegaly is a rare, chronic, and progressive disease characterized by excess secretion of growth hormone (GH) and elevated circulating levels of insulin-like growth factor 1 (IGF-1). It is predominantly caused by a pituitary adenoma. Clinical diagnosis is often delayed due to the insidious onset of symptoms related to GH excess. As a result, patients frequently present with established systemic complications, leading to increased morbidity and premature mortality. Measurement of serum IGF-1 is recommended as the initial screening test for suspected acromegaly. The gold standard diagnostic test is the oral glucose tolerance test with concomitant GH measurement. The treatment of acromegaly aims to lower GH and IGF-1 levels, improve patient symptoms, and reduce the local compressive effects of the pituitary adenoma. Therapeutic options include surgery, medical therapies (such as somatostatin receptor agonists, the GH receptor antagonist pegvisomant, and dopamine agonists), and radiotherapy. A multidisciplinary approach, often requiring combined treatment modalities, is recommended to control the disease and reduce associated morbidity and mortality.
In this study, we review the clinical presentations and treatment outcomes of acromegalic patients treated at our center over the past decade.

Keywords*: Acromegaly, somatotropic adenoma, hypothalamic-pituitary MRI, transsphenoidal surgery*

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I. Introduction

Acromegaly is characterized by a set of clinical, biological, and radiological signs related to abnormal secretion of growth hormone (GH). Its primary cause is a GH-secreting pituitary adenoma. If this occurs early in life (before the fusion of growth plates), it causes gigantism. The genetic causes of GH adenomas are partially elucidated [1,2,3].

Its annual incidence is 4-5 cases per million, with a prevalence of 28-137 cases per million [4]. The general consequences (cardiovascular, respiratory, metabolic, rheumatological, etc.) contribute to the disease's severity [5,6].

Transsphenoidal surgery is the primary treatment for GH-secreting pituitary tumors and is preferred, except for patients who are at surgical risk, refuse surgery, or have unresectable tumors.. Radiotherapy and medical treatment with somatostatin analogs are included to achieve clinical improvement and control of the disease.

In this study, we review the clinical presentations and treatment outcomes of acromegalic patients treated at our center over the past decade.

II. Patients And Methods

Type, period and location of the study

This is a retrospective, descriptive, analytical study, spread over 12 years, relating to the analysis of files of patients followed for acromegaly in Department of Endocrinology and Metabolic Diseases of Hassan II University Hospital in Fez.

Patients

The consultation of a database established in the service, made it possible to select 71 patients according to the following criteria:

Inclusion criteria

The inclusion criteria were patients over 16 years of age and biochemical confirmation of acromegaly from IGF-I levels for age [7] and unsuppressed nadir GH levels (>1 ng/mL) after an oral glucose tolerance of 75 g (OGTT) [8,9].

Exclusion criteria:

Were excluded from the study:
− Acromegaly under 16 years old
− Patients lost to follow-up

III. Methodes

We proceeded to an interrogation, a clinical examination and paraclinical examinations, and we collected the following variables:

Clinical and demographic data: Age; body mass index; blood pressure ;

Baseline clinical features included clinical presentations, comorbidities, family history. The duration of onset was estimated as the time interval between the clinical onset of disease and the time when the diagnosis was performed.

Laboratory measurements: measure for IGF-I, the oral glucose tolerance test (OGTT) GH , cortisol, adrenocorticotropic hormone (ACTH), free thyroxine (FT4), thyroid stimulating hormone (TSH), , follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone (T) estradiol (E2) , and prolactin (PRL).

Imaging data were studied by maximum diameter and invasion of tumor from magnetic resonance imaging (MRI) study. Tumor size was classified as microadenoma (<1 cm) and macroadenoma (≥ 1cm).

An ophthalmological evaluation based on visual acuity, the fundus and the visual field was carried out according to the context.

This study explored all employed treatment modalities; surgery, radiotherapy, medical treatments including dopamine agonists (DAs) or somatostatin analogs (SSAs).

Evolutionarily, treatment outcomes were categorized into 2 groups; group of controlled diseases defined by achievement biochemical remission criteria (standardized IGF-I levels for age and nadir GH levels ≤1 ng/mL (or 0.4) after a OGTT). Group of persistent diseases defined by no achieve biochemical remission of both IGF-I and GH level criteria.

In each group, clinical, biological and radiological parameters were identified (evaluation of pituitary functions, Hypothalamohypophyseal MRI at a rhythm adapted to each patient).

Statistical analysis: Retrospective study, carried out using SPSS version 25 software

IV. Results

During the period of our study, the total number of patients who responded to our inclusion criteria was 71 cases. The mean age at diagnosis was 48,55 ± 10,89 years with mean duration of onset of 5,56 ± 4,23 years. 70 % of our population were female, with a sex ratio (M/F) of 0.42

Clinical features at presentation: acrofacial dysmorphic syndrome 94% and pituitary tumor syndrome 35% were the two most frequent characteristics found in all the patients.

The other modes of discovery were a pituitary incidentaloma in 2% and an assessment of MEN 1 in 2% of cases. Vision was affected in about 40% of the patients, the fundus altered in 25% and impairment of the visual field was noted in 20% (dominated by bitemporal hemianopsia).

Hormonal evaluation and imaging studies: to at baseline, mean IGF-I levels were 712.66+/-270 ng/ml (3.44 LNS). The diagnostic confirmation was based on oral glucose tolerance test (OGTT) in 65% and a cycle of GH in 25% of cases. The hyperprolactinemia was present in 21%, hypogonadism in 19%, hypocortisolism in 15.4%, and thyrotropic insufficiency in 14%. On hypothalamic pituitary MRI, macroadenomas were predominant in 86% of cases and microadenomas in 14% of cases. Invasive tumors were found in 70 ,8 % of all patients.

Common co-morbidities were hypertension (34%), diabetes (34%),

Dyslipidemia (51%), sleep apnea (24%) and arthropathy in 96% of cases. Screening for tumors was revealed the presence of 30.57% of colon polyps, 2.81% of papillary thyroid cancers and no cases of colon cancer. Genetic syndrome with acromegaly was found in 2% of MEN1 cases.

Therapeutically, In first intention, transsphenoidal surgery (TSS), was conducted in 94% of patients, and medical treatment with somatostatin analogues was instituted in only 6% of cases. 39% of our patients were not controlled by the first-line treatment and benefited from a second-line treatment ((medical treatment in 59% of cases, radiosurgery in 30%, and a combination of radiotherapy and medical treatment in 11%).

68% of all cases operated (45.3% microadenomas, 22.7% macroadenomas) met remission criteria within 12 months of surgical treatment.

During follow-up, clinical improvement was noted in most cases. Postoperative evaluation complications showed diabetes insipidus in 2.81%, hypocortisolism in 46% (47% in controlled patients vs 45% in uncontrolled patients with non-significant p), hypothyroidism in 17% (15 % vs 20% with p not significant), hypogonadism in 33% (30% vs 36% with p not significant). Visual field recovery in 42.3%. In our controlled population, there was a significant improvement in arterial hypertension (12%), diabetes mellitus (16%) and dyslipidemia (8%) (Figure 1). Additionally, there was an improvement in the quality of life among controlled patients.

Paramètres	Acromégales Contrôlés	Acromégales Non contrôlés	P
HTA	12%	45%	< 0.001
Diabète sucré	16%	81%	
Dyslipidémie	8%	20%	
Insuffisance corticotrope	47%	45%	<0.09
Insuffisance gonadotrope	30%	36%	
Insuffisance thyréotrope	15%	20%	
Hyperprolactinémie	10%	14%	

Figure 1: Comparison of metabolic and hormonal parameters between controlled and uncontrolled acromegalic patients.

V. Discussion

Acromegaly is a rare, chronic, progressive disease characterized by an excess secretion of growth hormone (GH) and increased circulating insulin-like growth factor 1 (IGF-1).

Its annual incidence is 3 to 4 cases/million in the majority of studies [10].

The average age at the moment of diagnosis was 40 to 50 years [10] which agrees with the results of our series where the average age is 48.55 years ± 10.89. Regarding gender : Most studies have shown that there is no difference according to sex ,but this recent study from Korea showed that the incidence of acromegaly is slightly higher in women [11]. In our series, we note a female predominance in 70% of cases.

The mean time to diagnosis was 5,56 ± 4,23 years. In our series we found that the clinical features and presentations shared similarities with other studies **[9-10,12]**, and the symptomatology was dominated by dysmorphic syndrome and pituitary tumor syndrome.

On the cardiovascular level, this excess of GH and IGF1 is responsible for HVG, diastolic dysfunction, systolic dysfunction, arrhythmias, valvulopathy, and direct vascular injury **[13]**. The prevalence of hypertension is variable around 30% **[14]**, which is consistent with the results of our series.

The prevalence of sleep apnea syndrome is variable and can be observed in 100% of patients as shown in this Metaanalysis published in 2019 **[14]**. In our series, the prevalence of OSAS was 24%. This difference can be explained by the limited number of our patients having benefited from a polysomnography.

Carbohydrate intolerance and diabetes mellitus (DM) are the most common metabolic disorders and are present in 30% to 50% of acromegalic patients **[15]**. The prevalence of dyslipidemia is variable around 13-51% **[16]**. In our series, carbohydrate intolerance was observed in 17% of cases, the diabetes mellitus in 34% and dyslipidemia in 51%.

Arthropathy is a debilitating complication that negatively affects quality of life in acromegalic patients, and the prevalence of vertebral fractures is observed in 72.9 versus 20% in controls ($p < 0.001$) **[17]**. In our patients, arthropathy was reported in 96% and vertebral fractures in 2%.

The great concern of the clinician is to know the role of excess GH/IGF1 in carcinogenesis and tumor progression. In this large Italian multicenter cohort: the risk of cancer in acromegaly was found to be significantly increased (SIR 1.41 $p<0.001$), including colorectal cancer, thyroid cancer, and kidney cancer. And this increase in incidence seems to be more related to age than to excess GH **[18]**. Nevertheless, in our series, there were less cancers with only 2.8% of papillary thyroid cancers being found. the prevalence of anterior

pituitary insufficiency has recently decreased, this may be related to the improvement of surgical techniques, the generalization of pharmacotherapy, and the decline of radiotherapy over time

In our series, there was a predominance of gonadotropic insufficiency followed by corticotropic and thyrotropic insufficiency; with essentially disconnection hyperprolactinemia.

The therapeutic approaches in our series were surgery alone in the 94% of cases and associated with medical treatment or radiation therapy in approximately one third of case. Most of the articles published in the last two decades and using the same remission criteria than our study, showed 89% remission, 79% for microadenoma and macroadenoma, respectively in Japan [11] and 86.7%, 72.3% for microadenoma and macroadenoma, respectively in a Korean study [12]. In our series, 68% of all cases operated (45.3% microadenomas, 22.7% macroadenomas) met remission criteria within 12 months of surgical treatment.
Factors reported that may affect treatment results include male gender, advanced age, tumor size and IGF1 [5].

Another objective, in addition to obtaining biological remission, is the improvement of comorbidities. In this study published in 2020 **[19],** there is a decrease in overall cardiovascular system disorders and the risk of diabetes mellitus in controlled patients compared to uncontrolled patients. However, the risks of developing arthropathy, hypertension, LVH and OSAS were no different. In our controlled population, there was a significant improvement in arterial hypertension (12%), diabetes mellitus (16%) and dyslipidemia (8%) (figure). There was also an improvement in quality of life in controlled patients

These results underscore the importance of an integral approach when caring for these patients, focusing not only on monitoring GH and IGF-1 levels, but also on prompt diagnosis and specific treatment of each comorbidity.

VI. Conclusion

As this pathology is rare, it is difficult to carry out large series studies, which deprives endocrinologists of potentially very interesting deducible information only from larger numbers of patients.

This study provides the incidence of acromegaly, clinical, radiological presentations and results of the treatment at the CHU of FES . It shows favorable outcomes for patients, with only a few adverse complications demonstrated during the treatments.

Early diagnosis and adequate treatment of acromegaly are needed to mitigate excess mortality associated with this condition. Pituitary surgery is currently the cornerstone of management, with medical therapies and radiation therapy typically representing second- and third-line options, respectively.

New advances in our understanding of the pathogenesis of somatotroph adenomas are needed and could eventually lead to the development of new medical therapies. Other studies are necessary to provide us with solid and reliable criteria allowing us to predict response to medical care

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