

Long-Term Outcome of Patients with Acromegaly and Congestive Heart Failure

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Cardiovascular complications are a major cause of morbidity and mortality in patients with acromegaly. Normalization of GH secretion is associated with an improvement in structural and functional cardiac abnormalities. However, the long-term cardiac effects of treatment for acromegaly have not been studied in patients who have already developed chronic congestive heart failure (CHF).

We reviewed the charts of 330 consecutive patients with acromegaly treated in two French and Belgian centers since 1985. Ten patients with both acromegaly and CHF (eight men, two women, mean age 49.7 yr) were studied retrospectively. One of them was excluded because CHF was due to severe aortic stenosis.

CHF (New York Heart Association stages III-IV and echocardiography showing dilated hypokinetic cardiomyopathy with left ventricular systolic dysfunction and a left ventricular ejection fraction less than 45%) was diagnosed before, concomitantly, or after acromegaly in, respectively, two, five,

and two patients. Three patients were referred with terminal heart failure requiring transplantation.

One patient had transient CHF associated with a hypertensive crisis. The other eight patients had symptomatic chronic CHF. Control of GH hypersecretion failed, totally or partially, in three patients: one had a long-term survival, and the two others died at 1 and 5 yr. Good GH control was achieved in five patients: four of these are still alive 2–16 yr after diagnosis of CHF, their clinical status is stable or improved, and their quality of life is good. Overall, the 1- and 5-yr mortality (or transplantation) rates for patients with chronic symptomatic CHF were 25% (2 of 8 patients) and 37.5% (3 of 8 patients), respectively.

In conclusion, less than 3% of acromegalic patients developed CHF in this study. Although effective treatment of acromegaly improved short-term cardiovascular status, its impact on long-term survival is questionable. (*J Clin Endocrinol Metab* 89: 5308–5313, 2004)

CARDIOVASCULAR DISORDERS ARE the leading causes of morbidity and mortality in patients with acromegaly (1, 2). GH hypersecretion appears to have a direct detrimental effect on the heart, but other cardiovascular risks factors such as hypertension and diabetes mellitus are often associated (3, 4). Controlling GH hypersecretion can reverse some features of acromegalic cardiomyopathy such as myocardial hypertrophy and diastolic dysfunction (5, 6), particularly in patients younger than 45 yr (7), those with a short history of GH hypersecretion (7), and those in whom GH hypersecretion is controlled for more than 5 yr (8).

Diastolic dysfunction may lead to heart failure (9) in a subgroup of patients. However, generally speaking, patients with acromegaly complicated with heart failure have a congestive dilated acromegalic cardiomyopathy with systolic dysfunction. The vital prognosis for patients with congestive heart failure (CHF) was poor until the late 1980s (death within 1 yr), and treatment of acromegaly appeared ineffective (10). The advent of somatostatin analogs (SAs) led to a marked improvement in cardiac function in some patients

with CHF, but follow-up was short (no more than 3 yr) (11, 12).

The aim of this study was thus to determine the long-term cardiac effects of acromegaly treatment in patients with CHF.

Patients and Methods

Patients

We reviewed the charts of 330 consecutive patients with acromegaly followed up in two centers (Department of Endocrinology, Bicêtre University Hospital, le Kremlin-Bicêtre, France, and Department of Endocrinology, Liège University Hospital, Liège, Belgium), 10 of whom had CHF. One patient was excluded because CHF was due to severe aortic stenosis.

Acromegaly was diagnosed on the basis of consensus criteria (13). All nine patients had previously been treated for acromegaly (Table 1).

The diagnosis of CHF was based on clinical signs as described by the Framingham Heart Study group (14) and the New York Heart Association (NYHA) classification (for stages III and IV) and echocardiography showing a left ventricular ejection fraction (LVEF) of 45% or less (15–17).

Some data concerning short-term evolution have been previously reported (11, 12).

Methods

Detailed histories were obtained for each patient. Information on the treatment of acromegaly and its efficacy, other complications of acromegaly, long-term outcome, and the dates and causes of death was collected. Good control of acromegaly was defined by IGF-I normalization, a GH level less than 2 $\mu\text{g}/\text{liter}$, and suppression of GH by oral

Abbreviations: CHF, Congestive heart failure; EF, ejection fraction; LV, left ventricular; LVEF, LV ejection fraction; NYHA, New York Heart Association; SA, somatostatin analog.

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TABLE 1. Biochemical levels at the time of diagnosis and at the last visit during follow-up in nine patients with acromegaly and CHF

Patient no.	Sex/age (yr) at diagnosis of acromegaly	Basal hormonal levels		Treatments of acromegaly ^a	Time with good control of GH/IGF hypersecretion (yr)	Hormonal levels at the last visit during follow-up	
		GH	IGF-I			GH	IGF-I
1	M/34	60	900 ^b	S, SA	3	0.8	350 ^b
2	M/41	3.2	960 ^b	S, RT	6	<0.1	280
3	M/43	6.5	690 ^b	S, RT, SA	12	0.8	210
4	M/63	12	680 ^b	SA	2	4.5	220
5	M/59	264	NA	SA	Partial control	31	370 ^b
6	M/38	11	NA	SA	Partial control	3	260
7	F/59	6.9	670 ^b	S	5	3	180
8	M/47	39	550 ^b	S, SA	No control	45	510 ^b
9	M/62	10.2	330 ^b	S, SA	8	0.1	111

Upper limit of normal range for IGF-I according to age: 410 $\mu\text{g/liter}$ (30–40 yr), 375 (40–50), 315 (50–60), 285 (60–70), 265 (70–80), 155 (>80).

^aS, Surgery; SA, somatostatin analogs; RT, radiotherapy.

^bSupranormal levels of IGF-I; NA, not available.

glucose tolerance test (18). GH and IGF-II were assayed with commercial kits (19).

Because it was difficult to know the precise date of onset of acromegaly, we used the duration of uncontrolled GH between diagnosis and successful treatment.

Other diseases and cardiovascular risk factors were carefully reviewed. With regard to the cardiac history, changes in cardiac status on treatment and the results of serial echocardiographic measurements were analyzed. M-mode, two-dimensional, and pulsed Doppler echocardiographic studies were performed with commercial ultrasound systems, using a 2.5-MHz transducer during three to five consecutive cardiac cycles. The following measurements were recorded on M-mode trace (20): left ventricular (LV) end-diastolic diameter, end-systolic diameter, interventricular septum thickness, LV posterior wall thickness, LVEF, and fractional shortening. Cardiac catheterization and coronary angiography were performed in seven patients. Serial LVEF measurements (Table 2) were made by echocardiography.

Results

Characteristics of the patients at diagnosis of acromegaly and congestive heart failure

Nine patients (Table 1) among the 330 consecutive patients with acromegaly (2.7%) met the clinical and echocardiographic criteria for systolic heart failure (Table 2). CHF was diagnosed 1 and 10 yr before, concomitantly, and 11 and 14 yr after diagnosis of acromegaly in two, five and two patients, respectively.

At diagnosis of CHF, the NYHA classification was stages IV and III in seven and two patients, respectively. Basal echocardiographic findings in the nine patients are summarized in Table 2. Three patients (no. 5, 6, and 7) were referred for heart transplantation.

One patient (no. 9) had all the characteristics of CHF at presentation, but the immediate outcome suggested that latent asymptomatic LV dysfunction had been triggered by a hypertensive crisis. The other eight patients all had chronic CHF.

Basal echocardiography showed dilation of the LV, except in patient 9. Myocardial hypertrophy was present in four of the five patients for whom the relevant information was available. The LVEF was decreased in all the patients (mean 28.1%; range 11–45%) (Table 2). Diastolic parameters were not available at baseline. Systolic dysfunction with low cardiac output was confirmed by right ventricular catheterization in seven patients (data not shown). Individual risks

factors for cardiac disease and relevant comorbidities are detailed in Table 2.

No relation was found between severity of LV dysfunction [evaluated in terms of ejection fraction (EF)] and the time since CHF onset.

Cardiac outcome

Patient with precipitated heart failure. The patient whose heart failure was precipitated by a hypertensive crisis is still alive after 9 yr of follow-up. His EF (70%) remained stable.

Patients with chronic symptomatic CHF

Course of heart failure and LVEF. Follow-up ranged between 1 and 16 yr (mean 6 yr) in the eight patients with symptomatic CHF and systolic dysfunction. Two of them (no. 3 and 5) developed reversible atrial arrhythmias. They received maximal treatment for CHF (Table 2). LVEF improved significantly (>20% increase) in three patients, deteriorated significantly in two patients, and remained stable in the other three patients (Fig. 1). In patient 2, EF was initially 11% and increased to 45% after heart transplantation. No improvement in LV, diastolic diameters, or myocardial hypertrophy was observed by echocardiography during follow-up.

Short-term outcome

Cardiac outcome was poor during the first year of follow-up in two patients: one died suddenly (no. 8), and another required transplantation 4 months after the diagnosis (patient 2). This latter patient is still alive after 14 yr of follow-up. Thus, the mortality (or heart transplantation) rate at 1 yr was 25%. In the other six patients, treatment of acromegaly and heart failure markedly improved cardiac status, correcting congestive signs within a few months. Three and two patients reached NYHA stages II and III, respectively. Two patients (no. 1 and 7) returned to work (reaching NYHA stage I) and one patient (no. 1) tolerated a substantial reduction in cardiac pharmacotherapy (digitalis withdrawal and reduction in the diuretic dose).

TABLE 2. Cardiovascular characteristics at baseline and during follow-up in nine patients with acromegaly and CHF

Patient no.	Baseline (at time of CHF diagnosis)				Cardiovascular risk factors				Comorbidity	Cardiologic treatments	Duration (yr)	NYHA stage	Last LVEF	Outcome in 2003	
	NYHA stage		Echocardiography		HT	CHD	DM	Dysl.							
	Age	NYHA stage	H	D	LVEF	H	D	Dysl.							
1	48	III	+	+	20	+	-	-	-	COPD	D, ARA	3	I	55	Still alive
2	42	IV	+	+	11	-	-	+	+	SAS	D, ARA, B	0.3	I	45 ^a	Heart transplantation, 1989
3	54	IV	-	+	45	-	-	-	-	hT, AA	D, ACEI, Dig	16	I-II	32	Still alive
4	63	IV	+	+	33	-	+	-	-	COPD	D, ACEI, Dig, A	2	III	38	Still alive
5	58	IV	+	+	29	UK	-	-	-	AA	D, ACEI, A	5	I	16	Deceased-1990 (refractory CHF)
6	28	IV	UK	+	24	UK	+	-	-	-	D, ACEI, Dig	14	II	20	Deceased-1990 (refractory CHF)
7	59	III-IV	-	+	14	-	-	-	-	-	D, ACEI, A	6	II	53	Deceased-1998 (refractory CHF)
8	47	IV	UK	+	37	+	+	+	+	-	D, ACEI, B	1	II	40	Deceased-2002 (myocardial infarction)
9	62	IV	+	-	40	+	-	-	-	hT, SAS COPD	D, ACEI, B, Dig	9	II-III	68	Still alive (refractory CHF)

Echocardiography: H, ventricular hypertrophy (+, present; -, absent; UK, unknown); D, ventricular dilatation; LVEF, left ventricular ejection fraction (%). Cardiovascular risk factors: HT, hypertension; CHD, coronary heart disease demonstrated by angiography; DM, diabetes mellitus; Dyslip, dyslipidemia. Comorbidity: COPD, chronic obstructive pulmonary disease; SAS, sleep apnea syndrome; hT, hyperthyroidism; AA, atrial arrhythmia. Cardiovascular treatments: D, diuretics; ARA, angiotensin receptor antagonists; B, beta-blockers; ACEI, angiotensin-converting enzyme inhibitors; Dig, digitoxine; A, amiodarone. ^a LVEF after heart transplantation.

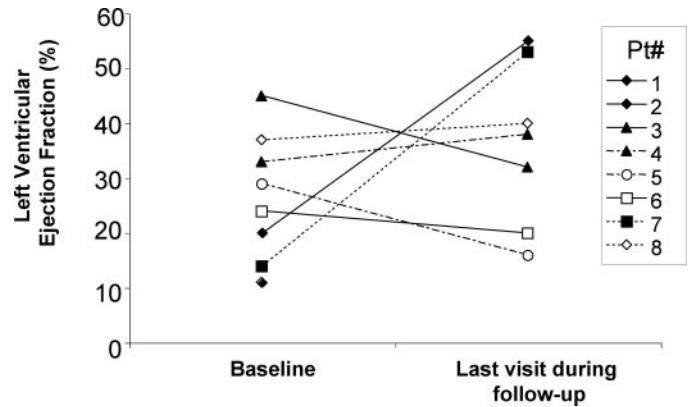


FIG. 1. Course of LVEF in patients with acromegaly and CHF. Values at baseline (at the time of diagnosis of CHF) and at the last determination during follow-up are presented. *Black and open symbols* indicate good and bad control of GH/IGF-I hypersecretion, respectively. In patient 2 the last EF value (45%) was obtained after heart transplantation.

Long-term outcome

At the last evaluation, five of the eight patients with CHF had died (n = 4) or undergone heart transplantation (n = 1). All the deaths were of cardiac origin (Table 2). The 5-yr mortality (or transplantation) rate was 37.5%.

Control of GH/IGF-I secretion and cardiac outcome (Fig. 2 and Table 1)

Control of GH hypersecretion was only partial in three patients: two had a poor cardiac outcome (no. 5 and 8); they died after 1 and 5 yr of follow-up, respectively. In the last patient (no. 6), referred 10 yr after the diagnosis of CHF, cardiac status improved markedly during the first 4 yr of SA therapy but then deteriorated, and he died of refractory CHF 14 yr after diagnosis of CHF. Strict control of GH hypersecretion with SA was achieved only during the last year of this patient's life.

Good control of acromegaly was achieved in five patients (no. 1, 2, 3, 4, and 7). IGF-I normalization was obtained in four patients (no. 1, 2, 4, 7) within the first months of SA therapy in three of them. In the fifth patient (no. 3), IGF-I normalized after 4 yr, thanks to radiotherapy and SA therapy. One of these five patients died after 6 yr of follow-up (patient 7). Patient 2 underwent heart transplantation and is still alive. The other patients are still alive.

Myocardial histology

Cardiac specimens were available in two cases. The explanted heart of the patient who was transplanted (no. 2) showed only endothelial fibrosis of coronary arteries; no intramyocardial fibrosis was found. The histological characteristics of the other patient, who had a cardiac biopsy before and 1 yr after effective treatment of acromegaly (no. 7), have been described in detail elsewhere (12): the first biopsy showed major myofibrilolysis and interfascicular fibrosis, both of which improved significantly after 1 yr of treatment with SA (Fig. 3).

FIG. 2. Individual long-term outcome in nine patients with acromegaly and CHF, according to time and control of GH/IGF-I hypersecretion. Time at diagnosis of acromegaly is indicated by a triangle; time at diagnosis of CHF is indicated by a closed circle. Plain line indicates good control and dotted line indicates bad control of GH/IGF-I hypersecretion. Arrows indicate that the patients are still alive, whereas death or heart transplantation is indicated by a vertical line.

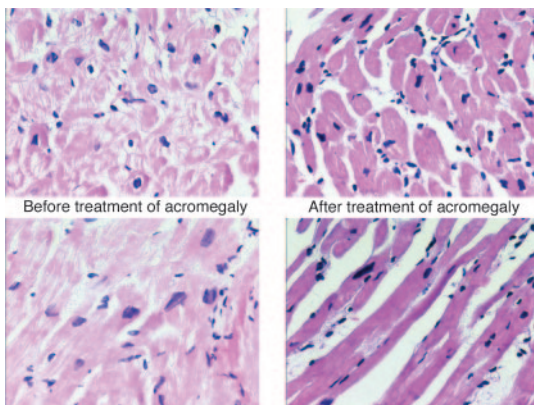
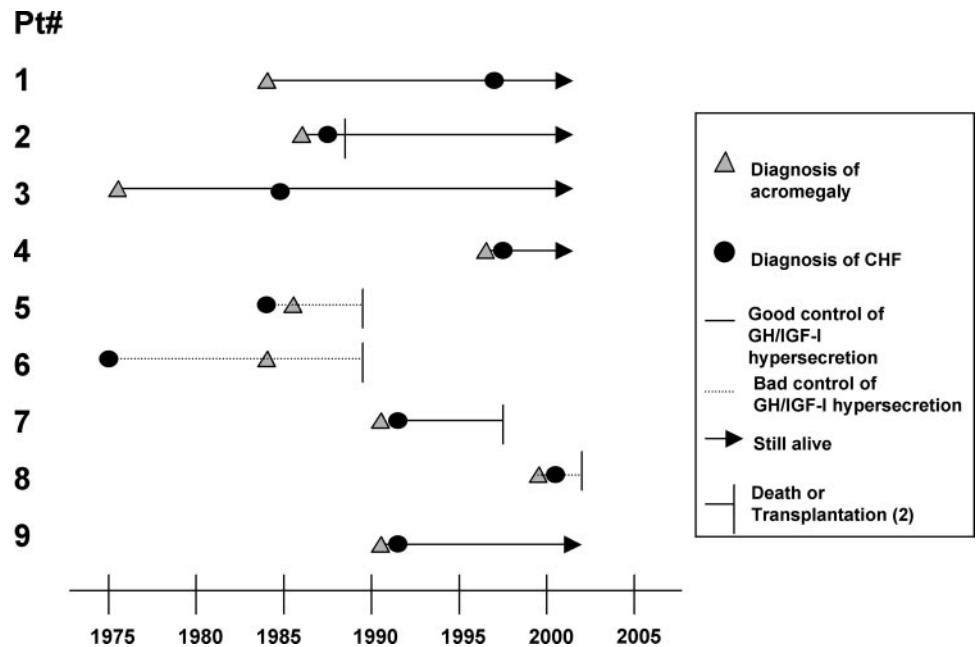


FIG. 3. Histological view of the heart obtained at myocardial biopsy in a patient with CHF before treatment and after cure of acromegaly. Before treatment (*left*) an extensive intracellular myofibrillarolysis with areas of myocytolysis and cellular infiltrate is observed. After the effective treatment of acromegaly (*right*), biopsy shows major regression of the disorders. [Courtesy of Albert Beckers, CD-ROM, Pituitary adenomas, 2003, Albert Beckers and GraphMed, Liège, Belgium.]

Discussion

Prevalence

Only 3% of patients with acromegaly in this series developed severe CHF. This figure is lower than generally reported (10, 21, 22), but these older studies were performed at a time when the treatment of acromegaly (and its comorbidities) was less aggressive and when CHF was diagnosed on the basis of less modern criteria and/or without the use of echocardiography. In addition, the treatment and follow-up of patients with acromegaly have improved markedly during the last two decades, and the risk of CHF is probably lower than before.

Pathophysiology

This small population of acromegalic patients with CHF was not very different from the general population of pa-

tients with acromegaly. Importantly, most of our patients had hypertension (eight of nine), although blood pressure control was good in most cases. Three of the nine patients had diabetes, a prevalence similar to that observed in the global population of acromegalic patients (4, 23, 24). The duration of uncontrolled acromegaly in our series was also similar to that observed in the general population of acromegalic patients (23, 24).

We found no specific risk factors for developing CHF in patients who were likely to have a previous common uncomplicated hypertrophic acromegalic cardiomyopathy.

The natural history of CHF in acromegaly is largely unknown (25). In the rat, chronic GH hypersecretion increases myocardial performance, improving cardiomyocyte contractility and reducing energy costs (26). However, cardiac hypertrophy and fibrosis eventually occur (3). We are aware of only one natural animal model of cardiomyopathy, reproducing the classical progression from acromegalic hypertrophic cardiomyopathy to ventricular dilation and systolic impairment (27). In humans, the duration of myocardial hypertrophy or ventricular dilation before CHF onset is unknown.

Prognosis of CHF

We chose to analyze separately the patient with transient CHF associated with an acute episode of hypertension, in whom LV function improved rapidly after resolution of the precipitating factor. Such factors can reveal asymptomatic LV dysfunction. Rapid recovery of LV function is associated with good long-term outcome (28).

The global prognosis of acromegalic patients with chronic CHF remains poor. In our series, the mortality/transplantation rate was 25% at 1 yr and 37.5% at 5 yr. These rates are very similar to those seen in patients with other causes of systolic heart failure (17, 29, 30) and suggest that the treatment of acromegaly fails to improve the long-term prognosis when acromegalic cardiomyopathy with LV systolic dysfunction is al-

ready present, confirming reports from McGuffin *et al.* (2) and Hayward *et al.* (10) a few years ago. Recently, Damjanovic *et al.* (9) reported similar, poor outcome among patients with early heart failure, but the criteria used to define CHF were not clearly defined in this paper. All our patients received near-maximal cardiologic treatment concomitantly with treatment for acromegaly, and it is therefore difficult to determine the prognostic impact of each treatment. Interestingly, the cardiac prognosis seemed to be similar whether or not treatment for acromegaly was effective: two of the five patients whose acromegaly was well controlled by medical therapy and two of the three patients with poor control had a poor outcome.

Cardiac hypertrophy and dilation may be irreversible once CHF occurs: treatment that lowers GH levels does not seem to improve cardiac structural abnormalities, contrary to what is observed in earlier stages of the disease (31–34), when good GH control can lead to regression of cardiac hypertrophy and improve both diastolic function (33–35) and exercise tolerance (increase in the exercise-induced EF increment) (36, 37).

Thus, at an advanced stage of cardiomyopathy, fibrosis, arrhythmias, and valve abnormalities may be irreversible. Lie (38) was the first to observe these abnormalities, in autopsy studies of acromegalic patients. This irreversibility could be due to chronic exposure to high GH/IGF-I levels, whereas lymphocyte infiltration could be reduced by treatment (12). One of our patients showed an improvement in myocardial histology (decreased myofibrilolysis and inter-fascicular fibrosis) during SA therapy.

Heart disease is generally considered to be the leading cause of mortality among acromegalic patients (1, 24). Two sudden deaths occurred in our series, one in a patient known to have ventricular arrhythmia. The prevalence of arrhythmias is probably underestimated in acromegaly (39); they can be corrected when GH hypersecretion is controlled (40, 41). Because CHF seems to be rare, most cardiac deaths would appear to be due to arrhythmias; 24-h electrocardiographic recording was recently recommended in a consensus statement on acromegalic complications (42).

Although the long-term prognosis of CHF remains poor in patients with acromegaly, some patients show an immediate improvement in clinical status and an increase in the LVEF when treatment for acromegaly is started, possibly owing to the marked reduction in extracellular volume when GH hypersecretion is controlled (review in Ref. 43). Diuretic treatment may thus have a synergistic beneficial impact on cardiac status. Specific treatment of chronic heart failure may also help to improve cardiac function. Angiotensin-converting enzyme inhibitors and β -blockers are used to limit cardiac remodeling (44), and they have proved to be effective in reducing mortality and morbidity in patients with heart failure of various causes (45–47). Whether treatment of acromegaly has an impact on myocardial contractile function at this stage of the disease is presently unknown.

Intensive management of these patients with severe cardiac disease (regular visits, dietary advice, verification of treatment adherence, treatment of comorbidities, *etc.*) no doubt contributes to improving vital outcome. Correction of arrhythmias (which may precipitate heart failure) may be sufficient to improve the ejection fraction (48).

In conclusion, CHF is a rare complication of acromegaly,

occurring in less than 3% of patients. The vital prognosis is variable. When an acute episode such as a hypertensive crisis or arrhythmia precipitates transient CHF, with rapid recovery of myocardial dysfunction, initial cardiac status is generally recovered and is maintained by effective management of acromegaly. In contrast, patients with CHF, chronic dilated cardiomyopathy, and LV systolic dysfunction have a poor prognosis, similar to that of patients with CHF of other causes. Indeed, the mortality (or transplantation) rates in our series were 25% at 1 yr and 37.5% at 5 yr. Treatment of acromegaly seems to improve cardiac function in the short term but probably has little or no effect on myocardial hypertrophy, ventricular dilation, or the long-term prognosis. This indicates that myocardial damage is irreversible at this stage of acromegalic cardiomyopathy. These patients therefore need optimal therapy for heart failure and effective prevention of sudden death due to cardiac arrhythmia.

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