

CARDIOVASCULAR RISK IN ACROMEGALY

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Abstract

Acromegaly is associated with cardiovascular disease, the principal cause of increased mortality. Direct cardiac effects of GH/IGF-1 are cardiomyocyte growth and cardiac contractility, cardiac remodeling. Other important risk factors in acromegaly are hypertension, valvular diseases, arrhythmias. Older patients with long-term uncontrolled disease may develop congestive heart failure as end-stage of acromegalic cardiomyopathy. Early treatment of acromegaly is essential for evolution and prognosis of cardiovascular complications.

Keywords: *cardiomyocyte growth, cardiomyopathy, hypertension, valvular diseases.*

Rezumat

Acromegalia se asociază cu boala cardiovasculară, care este cauza principală a mortalității crescute. Efectele cardiace directe ale GH/IGF-1 produc creșterea cardiomiocitelor, a contractilității cardiace și remodelare cardiacă. Alți factori de risc importanți în acromegalie sunt: hipertensiunea arterială, bolile valvulare, aritmiile. Pacienții cu boală necontrolată pe termen lung pot dezvolta insuficiență cardiacă congestivă, ca stadiu final al cardiomiopatiei acromegalice. Tratamentul precoce al acromegaliei este esențial pentru evoluția și prognosticul complicațiilor cardiovasculare.

Cuvinte cheie: *creșterea cardiomiocitelor, cardiomiopatie, hipertensiune, boli valvulare.*



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Acromegaly is a rare pituitary disease, characterized by an excess of growth hormone (GH)⁽¹⁾. The exposure to high concentrations of GH produces gigantism in children and acromegaly in adults. Acromegaly is produced in most cases (99%) by a pituitary adenoma that secretes GH, which occurs sporadically or as part of a syndrome of multiple endocrine neoplasia type 1 (MEN) and acromegaly/gigantism is the second most frequent among pituitary adenomas, representing approximately 17% of these. Acromegaly has an annual incidence of 3-4 cases/1 million/year and a current prevalence of 40 cases/1 million, that can reach up to 130 cases/1 million.

GH and IGF-1, known mostly as regulators of longitudinal growth of bones, are multifunctional growth factors. After growth stops, GH continues to have a physiological role in the body; GH and IGF-1 have a positive effect on body composition, muscle force, bone mineral density, reproductive capacity, skin properties, and metabolic functions.

The existence of a connection between acromegaly and the heart has been recognized for a long time, and the effects of GH and IGF-1 on the regulation of cardiac growth and on maintaining the heart structure are the object of some in-depth studies. Experimental models on animals with GH excess induced either by GH-secreting tumors, or by exogenous

administration of high doses of GH or IGF-1, have demonstrated the hypertrophic response of the left ventricle, with an increase of cardiac function, both *in vivo* and *in vitro*.

Human and animal studies proved that the GH - IGF-1 axis is involved in the regulation of myocardial structure and function. In particular, a large number of studies show that GH and IGF-1 are deeply involved in the growth of cardiomyocytes. The effects of GH-IGF-1 have been documented experimentally and clinically in conditions of GH deficiency, cardiomyopathy, ischemia-reperfusion. The administration of GH, GH secretagogues and IGF-1, alone or in combinations, improves cardiac function both in normal hearts and in insufficient ones. Conversely, there have been reports of an increase in morbidity and mortality after the administration of high doses of GH in critical patients. Also, high levels of GH in acromegaly produce a specific cardiomyopathy and cardiac dysfunction, with an increase of morbidity and mortality in acromegalic patients.

Early diagnosis and treatment can prevent the irreversible changes associated with the overproduction of GH and IGF-1 and can improve life expectancy, considering that the mortality rate in patients with acromegaly is 2-4 times higher than that of the healthy population, due to systemic complications of hypersomatotropism. Due to insidious

evolution, the diagnosis of acromegaly is usually delayed by a varying number of years. Therefore, retrospective epidemiological studies have shown that the diagnosis can be preceded by the active disease by approximately 4-10 years, or even more. Knowing these risks, morphological and functional cardiac assessment is recommended for all patients with acromegaly.

Cardiovascular morbidity and mortality are high, and cardiovascular disease is the main cause of premature mortality in acromegaly. These correlate with the excess plasma levels of GH and IGF-1, which induce a specific cardiomyopathy with ventricular remodeling, and that can sometimes lead to chronic heart failure. Generally, cardiomegaly becomes symptomatic late, after other signs of the disease are evident. Late diagnosis, usually after 5-10 years from the first manifestations, influences the progression of the disease and the occurrence of complications^(1,2,3,4).

The causes of mortality are, in order of frequency:

- 60% deaths of cardiovascular causes
- 25% deaths due to respiratory diseases
- 15% deaths due to malignancy

High levels of GH, hypertension and cardiac disease are the negative determinants for survival, while other factors (the duration of the symptoms, unbalanced diabetes, dyslipidemia, cancer) have little effect on mortality.

For that reason, the decrease of mortality rate can be achieved by:

- controlling GH hypersecretion;
- controlling cardiac disease;
- controlling hypertension.

GH values are considered the best predictive indicator for survival. There is evidence that normalizing the levels of GH and/or IGF-1 is associated with an improvement of mortality rate, independently of associated complications^(1,2).

Acromegalic cardiomyopathy has been recognized since the first descriptions of the disease, in the late XIX century. Cardiac changes characteristic for acromegaly are hypertrophy, fibrosis, diastolic dysfunction, decreased systolic function during effort with decreased exercise tolerance and systolic dysfunction at rest, in rare cases with prolonged evolution also in the absence of treatment.

The main histological anomalies described in the acromegalic heart are left ventricular hypertrophy and interstitial fibrosis, and the fibrosis seems to be a consequence of focal myocyte necrosis. Left ventricular hypertrophy is present in most patients at the time of the diagnosis, but mainly in those with a prolonged evolution, in up to 70% of patients with normal blood pressure and in 90% of patients with hypertension⁽⁵⁾. LV hypertrophy and the impairment of LV function are also related to the level of GH and IGF-1, age and duration of the disease⁽⁵⁾. In these cases, from a histological point of view, there is a disruption of the architecture via an increase of extracellular collagen deposits, myofibrillar disruption, areas of monocyte necrosis and lymphomononuclear infiltrate, which leads to a pattern of myocarditis. In some patients, small vessel disease has been described. The increase of apoptosis in cardiomyocytes and interstitial fibroblasts has been found in biopsies obtained during cardiac catheterization in acromegalic patients. The degree of apoptosis and fibrosis is positively correlated with the duration of the disease^(5,6,7,8).



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Cardiomiopatia acromegalică. Istoria naturală.

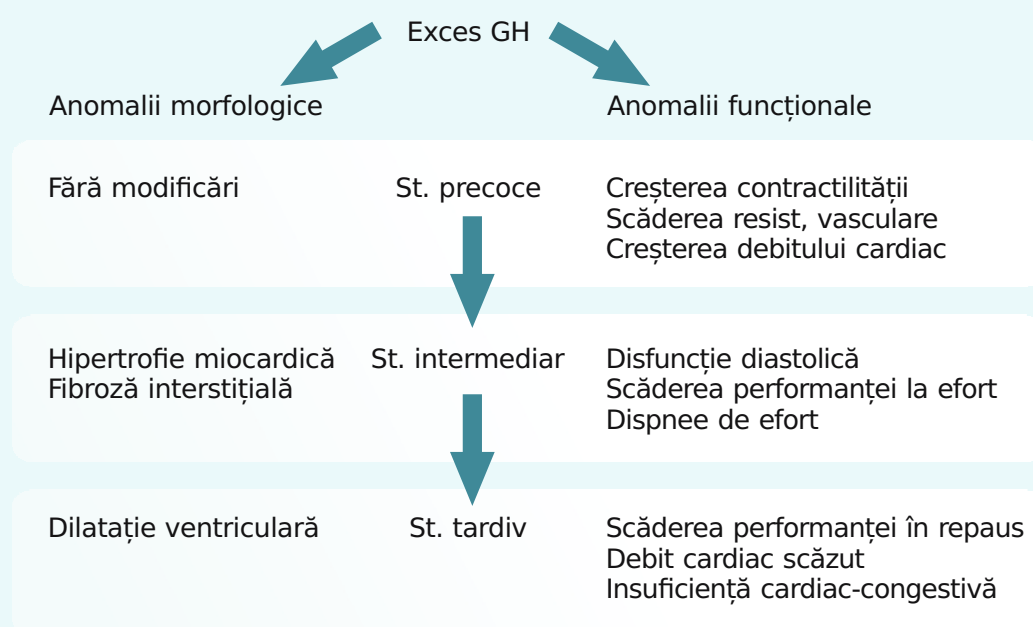
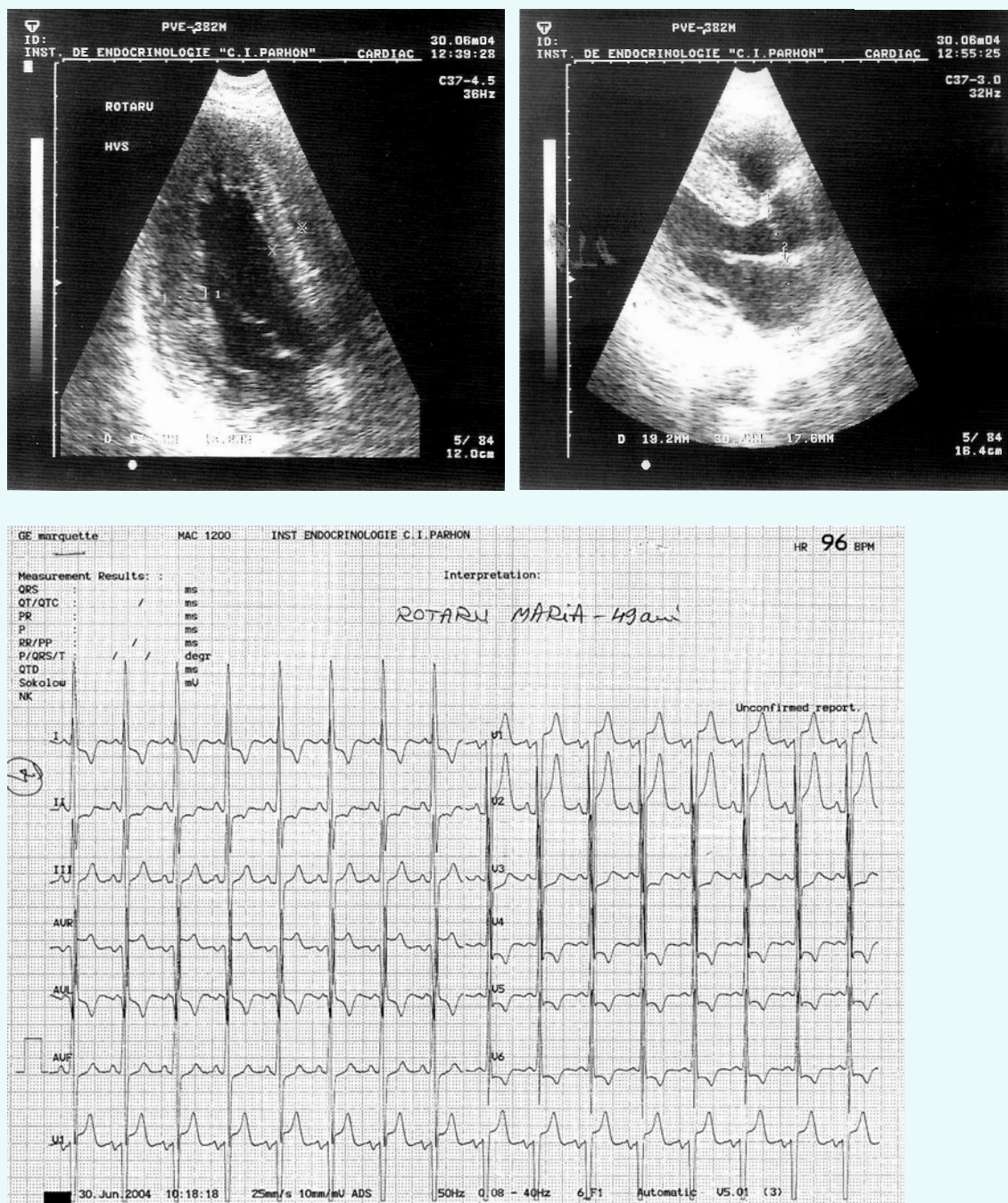


Figure 1. The natural evolution of acromegalic cardiomyopathy

In patients with cardiac dilatation, myocyte death and collagen deposits are in high quantity on endomyocardial biopsy specimens and it seems that myocyte death, via apoptosis and necrosis, contributes to ventricular remodeling, the onset of ventricular dysfunction and its progression to heart failure. Moreover, it has been hypothesized that the abnormal regulation of the extracellular matrix via overproduction of GH or IGF-1 in patients with acromegaly can contribute to systolic and diastolic myocardial dysfunction; also, GH can

increase the levels of circulating pro-inflammatory cytokines^(7,8).

The natural history of acromegalic cardiomyopathy can have a slow evolution, with several stages⁽¹¹⁾. In the early stage, cardiac performance is not impaired and cardiac output is even high, heart rate is high, vascular resistance is low and thus contributes to the development of a hyperkinetic syndrome. In acromegaly, the heart walls are thickened and the heart chambers are more rarely dilated, the most frequent cardiac functional disorder is the



Figures 2, 3, 4. RM, 49 years old. Late-diagnosed pituitary adenoma, with subsequent surgery and radiation therapy. LVH. Hypertrophic nonobstructive cardiomyopathy, IVS 17 mm, post. wall 16 mm, LV diastolic dysfunction, LVEF 57%



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relaxation disorder and the inadequate ventricular filling capacity. This leads to a diastolic ventricular pattern of delayed relaxation and to an increase of the ventricular stiffness as a result of myocardial hypertrophy and interstitial fibrosis. Diastolic dysfunction via delayed relaxation of ventricular myocardium sets in and, additionally, the systolic LV function during exercise is compromised.

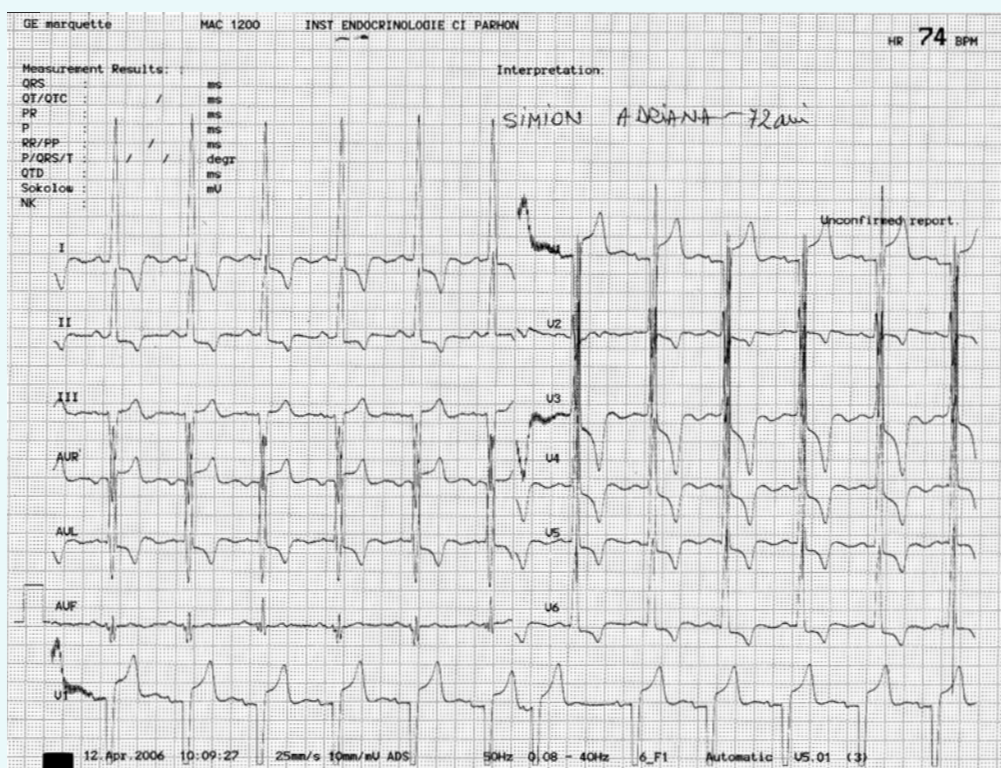
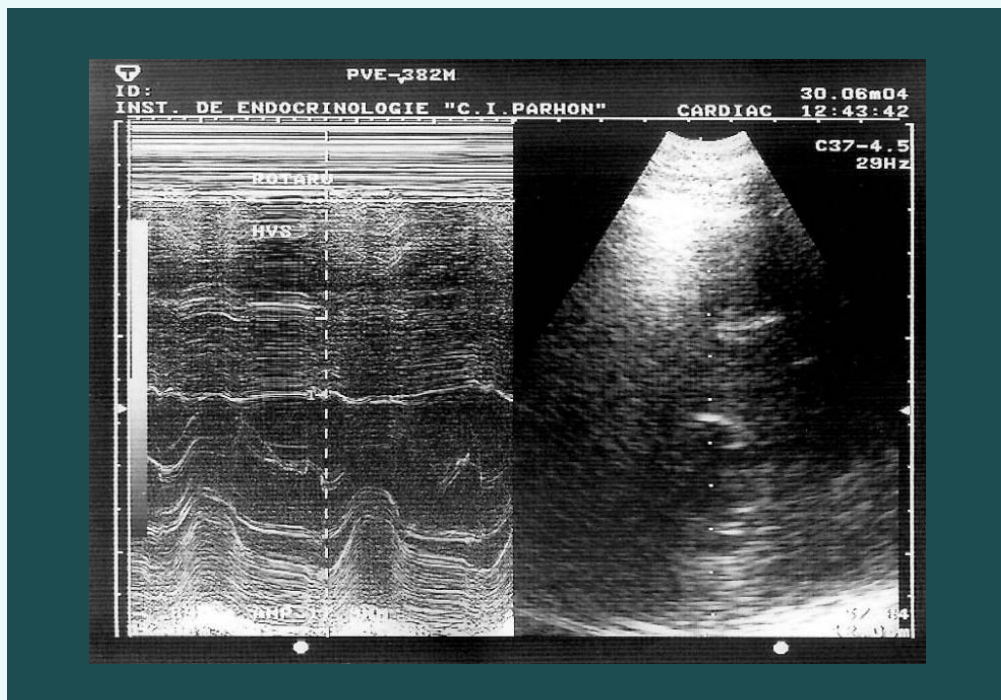
After a long evolution and in the absence of treatment, acromegalic cardiomyopathy evolves with ventricular dilatation, systolic dysfunction at rest and clinical signs of heart failure with low LV ejection fraction. Currently, this type of evolution occurs in increasingly rare cases, with long evolution also in the absence of treatment, an evolution seen in approximately 3% of acromegalic patients⁽⁹⁾. In the late stage, in patients with a long history of the disease and in the absence of treatment, the clinical presentation is characterized by:

- Hypertrophy of heart walls +/- dilatation of heart chambers⁽⁹⁾
- Valvular diseases
- The decrease of systolic and diastolic performance, with low cardiac output at rest
- Chronic heart failure can be present in untreated cases and with a long evolution.
- Rhythm and conduction disorders.

In time, the ventricular dilatation with the alteration of global cardiac performance, even at rest, as well as the decrease of cardiac output lead to congestive heart failure. Currently, this type of evolution is seen increasingly rarely (in up to 3% of patients) and is limited to patients with acromegaly who are untreated and with a long evolution. Also, coexistence with other complications, especially hypertension and diabetes mellitus, worsens the evolution of acromegalic cardiomyopathy.

Hypertension is considered one of the most relevant negative prognostic factors in acromegaly and its incidence is approximately 30-40% of patients with acromegaly⁽¹⁷⁾. The pathophysiological mechanisms that can contribute to the development of hypertension are partially known, but a myriad of factors is incriminated^(18,19,20,21,22,23,24,25,26,27,28,29,30,31,32):

- the increase of plasma volume and of sodium turnover;
- insulin resistance with hyperinsulinemia and diabetes mellitus;
- the renin-angiotensin-aldosterone system
- the atrial natriuretic peptide;
- the adrenergic system;
- the increase of cardiac output and of the cardiac index;
- alterations of systemic vascular resistance and heterogenous



Figures 5, 6. S.A., 72 years old; Recently-diagnosed pituitary adenoma, untreated Hypertrophic obstructive cardiomyopathy: IVS 23 mm, LV 21/31 mm, EF 54%, left ventricular diastolic dysfunction



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distributions of the cardiac output - abnormalities that could be responsible for the increase of the thickness of vessel wall, endothelial dysfunction and/or the dysregulation of arterial tone;

- sleep apnea.

Valvular diseases, mitral and/or aortic, can frequently complicate the evolution and the prognosis of patients with acromegaly (22% of cases compared to 6.7% in the rest of the population) and the prevalence of valvular lesions correlates with the duration of the disease.

The valvular lesions in acromegaly are related to the direct effect of GH and IGF-1 on the conjunctive tissue, with a dysregulation of metalloproteinases expression, proteoglycan synthesis and collagen and mucopolysaccharides deposition. It has been hypothesized the pathogenesis of the myxomatous valvular degeneration, with the activation of valvular interstitial cells, the release of proteolytical enzymes, proliferation; subsequently, the degradation of collagen, the fragmentation of elastin and the accumulation of glycosaminoglycans, that would possibly produce the remodeling of the extracellular matrix and the characteristic change of the myxomatous valve, with thickening and redundancy.

The most frequent lesion is aortic

regurgitation, with a prevalence of 30% of cases and even higher. This process could correlate especially with the duration of evolution of the acromegaly, with reports of a prevalence of up to 10% in acromegalic patients with a duration of the disease of maximum 10 years and an increase in prevalence to 35-38% in patients with an evolution of over 15 years (an increase of 19% in the risk of valvular disease has been reported for each year of acromegaly evolution)^(10,12).

The presence of mitral and aortic annular dilatation, frequent in acromegaly, worsens the evolution of valvular diseases in acromegaly and correlates positively with the left ventricular mass and the duration of evolution of the disease⁽¹²⁾.

Rhythm and conduction disorders can be present in acromegaly, favored by myocardial hypertrophy and fibrosis, and represent a major risk factor. Ventricular rhythm disorders occur in conditions of the ventricular remodeling, and their frequency and severity increase with the duration of the evolution of the disease, the ventricular mass and the GH level. The prevalence of late potentials is high in patients with active acromegaly and is related to the duration of the disease. Late potentials as predictor of ventricular arrhythmias occur in relation to the disorganized myocardial architecture and

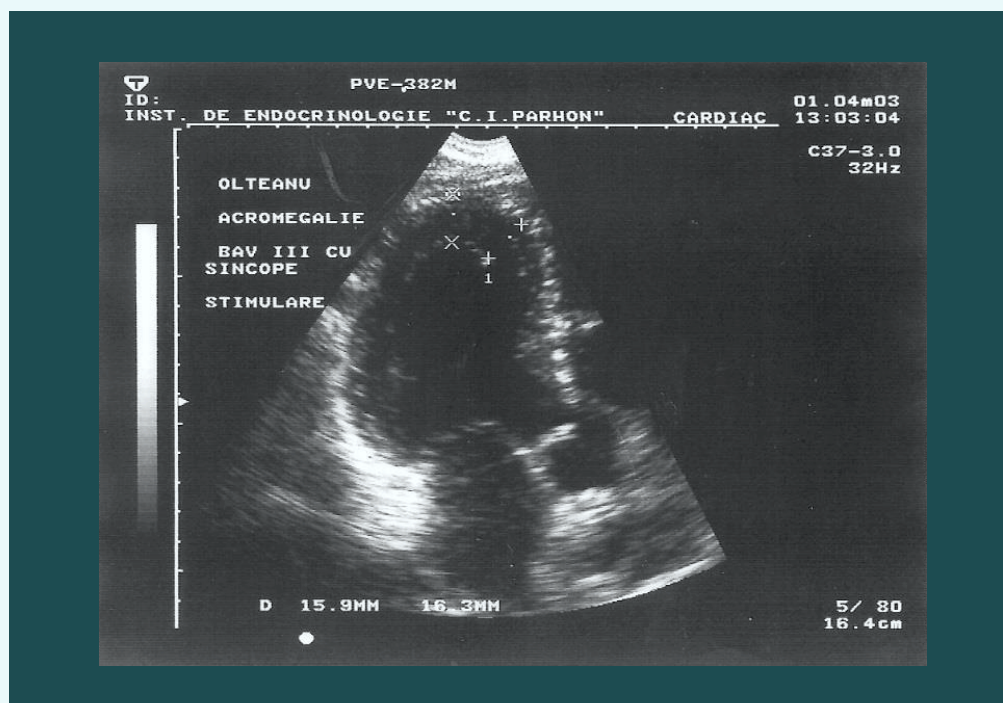


Figure 7. O.S., 62 years old. Late-diagnosed acromegaly. Advanced acromegalic cardiomyopathy. LV hypertrophy: SIV 16 mm, ant. wall 15 mm, post. wall 15 mm
LV dilatation: 59/70 mm EF 44%
Mitral regurgitation grade I-II; aortic regurgitation grade I-II
Permanent cardiac pacing for third degree AV block with syncope

the asynchronous electrical activity in acromegaly (areas of hypertrophic myocytes, separated by fibrosis and cellular infiltrates). The presence of late potentials correlates with the occurrence of severe ventricular tachyarrhythmias and is associated with a high risk of sudden death in acromegaly. There are rare cases presented in literature of sudden death in patients with acromegaly and the autopsy examination of conductive tissue revealed fibrolipomatosis, the dispersion of the atrioventricular node, the sclerosis and the lipomatosis of the right branch^(13,14,15,16).

The effect of controlling GH and IGF-1 on the cardiovascular disease in acromegaly is addressed in a multitude of studies that suggest that normalization of plasma levels

of GH and IGF-1 may stop the progression of cardiac disorders in acromegaly, reducing the cardiovascular mortality. However, the evolution of the cardiac disease in patients with acromegaly after various therapeutic interventions is variable and irregular^(33,34,35,36).

The results of the study

Our team presents the experience gathered in this field, considering the volume of activity and the diversity of cases in the C.I. Parhon Institute of Endocrinology. We present a group of 28 patients, 9 women and 19 men, aged between 37 and 67, assessed and treated in the Institute of Endocrinology between 2011 and 2017. The duration of the occurrence and of evolution of symptoms before establishing the diagnosis has been



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estimated at between 5 and 12 years, the real onset of the disease being determined based on subjective and objective personal history items. The cardiological assessment detected 7 patients with chronic heart failure, 7 patients with hypertension, 5 patients with diabetes mellitus, 4 patients with permanent atrial fibrillation, significant left ventricular hypertrophy in all patients. This was due to the significant increase in LV size and wall thickness, therefore the relative wall thickness did not change. In agreement with the Framingham study, the LV mass increase was correlated with a high incidence of cardiovascular clinical events, including deaths. The ultrasound study of patients detected significant changes. The LV mass index is high in most patients (25 patients).

Ventricular diastolic dysfunction in acromegaly represents a cause of decreased cardiac performance during exercise and predicts systolic dysfunction. In acromegaly, the heart walls are thickened and the heart chambers are more rarely dilated, the most frequent cardiac functional disorder being represented by the inadequate ventricular filling capacity. This leads to a diastolic ventricular pattern of delayed relaxation and to an increase of the ventricular stiffness as a result of myocardial hypertrophy and interstitial fibrosis. In the cases studied by our team, the LV diastolic filling disorders were present in 81% of the cases.

In acromegaly, a multitude of studies prove the decrease of cardiac functional reserve, progressive in relation to the duration of the disease and to the exposure to high values of GH - IGF-1. Therefore, although at rest these patients have a normal EF and are asymptomatic, during exercise the EF remains unchanged (compared to the increase of EF during exercise in non-acromegalic people).

In the presented lot, the LV ejection fraction (EF) was variable between 55% and 62% in those with normal heart function (72%) and between 38% and 48% in patients with congestive heart failure (28%); the decrease of LVEF below 48% was seen in patients aged over 50, with a long evolution of acromegaly and late diagnosis.

Generally, ventricular dilatation and the decrease of global cardiac performance, with low cardiac output and clinical presentation of heart failure, is a late stage of acromegalic cardiomyopathy and occurs in patients with a long evolution. Cardiac ultrasound studies combined with radionuclide angiogram indicated a decrease of 40% in the ejection fraction during exercise in 73% of patients with acromegaly (42% of cases aged <40 and 95% aged >40).

In the presented cases, congestive heart failure was diagnosed in 7 patients, all aged over 45; at the time of diagnosis, CHF was class III-IV NYHA in 25% of patients, all having

had late-diagnosed acromegaly, long evolution and cardiac morphological and functional changes: LV hypertrophy 7 patients, LV dilatation 6 patients, LVEF <48% 6 patients.

Rhythm and conduction disorders are an aggravating factor in acromegalic cardiomyopathy. In our lot, 12 patients were recorded with polyfocal ventricular extrasystoles and in bursts, all aged >45 years, 2 patients presented episodes of ventricular tachycardia during Holter ECG recording, 4 patients already had permanent atrial fibrillation at the time of diagnosis. 6 patients presented conduction disorders: a patient with first degree AV block, a patient third degree AV block, two patients third degree RBBB, two patients with third degree LBBB; the patient with third degree AV block and a history of syncope received permanent pacing at Floreasca Emergency Hospital.

Valvular diseases have been diagnosed in 4 patients. In our lot, moderate aortic regurgitation was detected in 14% of patients in the <45 year old group and in 32% in the >45 year old group and moderate mitral regurgitation in 12% in the <45 year old group and in 26% in the >45 year old group.

These data support the idea that a long exposure to high levels of GH - IGF-1 has destructive effects on cardiac performance and on the vital risk of patients.

Conclusions

The cardiac disorder in acromegaly can be asymptomatic for many years before the occurrence of clinical manifestations. Myocardial hypertrophy is present in over 50% of patients at the time of diagnosis and the prevalence increases up to 100% when hypertension is also associated; it is present in most patients at the time of diagnosis and

is generally more severe in patients with a longer history of disease, in which interstitial fibrosis represents the main histological anomaly. If acromegaly is inadequately or late-treated, cardiomyopathy can evolve with ventricular dilatation and heart failure. In advanced stages of cardiomyopathy, the fibrosis, the arrhythmias, the valvular abnormalities are irreversible and the consequences are unpredictable.

The study presented by our team confirms the fact that the cardiac involvement occurs already in the early stages of the disease: the presence of left ventricular hypertrophy in a significant percentage (47-52%) of patients aged <45, with a shorter history of disease, demonstrates that cardiac structural alterations can occur after a short exposure to GH hypersecretion. In the presented lot, the cases that developed congestive heart failure generally had a long history of acromegaly and were in general late-diagnosed, associated valvular regurgitations and a decrease of systolic and diastolic performance.

Other abnormalities, such as hypertension, coronary artery disease, ventricular arrhythmias, can worsen the cardiac function. Heart disease is considered to be the main cause generating death in patients with acromegaly and sudden death can occur, especially due to arrhythmias. As a matter of fact, the prevalence of arrhythmias is probably underestimated in acromegaly⁽³⁶⁾.

The assessment of prognosis in patients with acromegalic cardiomyopathy is difficult, but it can be correlated with: the estimated duration of the disease, the patient's age, the presence of coronary artery disease and of hypertension at the moment of diagnosis, the presence of arrhythmias, the plasma level of GH. The coexistence of additional risk factors can accelerate the progression towards dysfunctional cardiomyopathy. Therefore,



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the morphological and functional cardiac assessment at the time of diagnosis of the patient with evolving acromegaly, is essential for the management of these patients.

In the presented lot, the cases that developed congestive heart failure generally had a long history of acromegaly and were in general late-diagnosed, associated valvular regurgitations and a decrease of systolic and diastolic performance. The treatment of acromegaly seems to improve the cardiac function in the short term, but its effects are probably modest or absent on myocardial hypertrophy and on ventricular dilatation in the long term. The intensive management of patients with severe cardiac lesions contributes to improving the vital prognosis. Also, the correction of arrhythmias, which can precipitate the heart failure, can be sufficient to improve the ejection fraction.

These data indicate the fact that myocardial lesions are irreversible in this stage of acromegalic cardiomyopathy and therefore an early diagnosis of the disease is required. In late stages, patients require optimal therapy for heart failure, up to heart transplant, as well as the efficient prevention of sudden death due to cardiac arrhythmias.

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