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Pituitary diseases: long-term clinical consequences

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Chapter 2

Uncontrolled Acromegaly is Associated with Progressive Mitral Valvular Regurgitation

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ABSTRACT

Introduction

Recent cross-sectional studies have documented an association between acromegaly and regurgitant valvular heart disease. The aim of this study was to evaluate the change in prevalence of valvular heart disease in relation to the clinical activity, because the natural history of valvular changes in acromegaly is unknown.

Patients and methods

Valvular regurgitation was assessed in 37 acromegalic patients (18 patients with active disease, and 19 with controlled disease) by conventional two-dimensional and Doppler echocardiography before and after an interval of 1.9 yr (range 1.5-3.0 years).

Results

At baseline, valvular regurgitation (mitral and aortic sites combined) was present in 46% of the patients and increased to 67% at follow-up (p=0.008). Mitral regurgitation increased significantly from 32% to 60% (p=0.002), but no change was noted for the aortic valve (27 vs. 31%, NS). In patients with active disease, valvular regurgitation increased significantly from 56% at baseline to 88% at follow-up (p=0.031) due to a significant increase of mitral regurgitation from 39% to 78% at follow-up, p=0.016). In contrast, no increase in valvular regurgitation was found in patients with controlled disease.

Conclusion

The prevalence of mitral, but not aortic, valvular regurgitation increased in patients with active acromegaly during follow-up. Patients with acromegaly require adequate cardiac evaluation and follow-up to establish the extent and progression of valvular involvement.

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INTRODUCTION

Active acromegaly alters cardiac structure and function. Cardiac manifestations of acromegaly include left ventricular (LV) hypertrophy, arrhythmias, and heart failure due to diastolic and systolic dysfunction (1-3), but fortunately adequate treatment of growth hormone excess can arrest or even reverse these cardiac changes (4).

Recent cross-sectional studies have documented an association between acromegaly and regurgitant valvular heart disease, irrespective of disease activity (5;6). In these studies it was concluded that valvular change is apparently irreversible in contrast to the observed regression of LV changes in successfully treated patients. Because the natural history of valvular changes in patients with acromegaly is unknown, the aim of the present observational study was to evaluate the changes in prevalence of valvular heart disease in relation to the clinical activity. Therefore, we enrolled patients previously described in our cross-sectional study (5) and reassessed valvular regurgitation after an interval of at least 1.5 years. In order to assess the possible influence of disease activity on valvular disease, we studied patients with (mild) active disease and patients with controlled disease. We hypothesized on the basis of the high prevalence of valvular regurgitation found in our cross-sectional study that valvular regurgitation would increase during follow-up in patients with active disease.

PATIENTS AND METHODS

Patients

Thirty-seven patients were enrolled to this study, of whom 35 had participated in the previous study (5). The initial diagnosis of acromegaly was based on the characteristic clinical features and confirmed by insufficient suppression of GH during a glucose tolerance test (normal response: GH nadir <0.5 µg/L), an elevated age- and gender-adjusted IGF-I, and the presence of a pituitary adenoma on radiological imaging.

Patients were classified at study entry as having active or inactive acromegaly.

Active acromegaly (n=18) was defined as: mean fasting GH concentration (measured every 30 minutes for 3 hours) >2.5 µg/L, and an elevated age- and gender-adjusted IGF-I concentration. This study was performed before the introduction of GH receptor blockade drugs. Nineteen patients were classified as inactive acromegaly which was defined in medically well-controlled acromegaly (n=13) as mean fasting GH concentration (measured for 3 hours with an interval of 30 minutes) <2.5 µg/L, and normal age- and gender-adjusted IGF-I concentrations during treatment with depot octreotide acetate (n=13, Novartis Pharma AG, Basel, Switzerland) and in surgically cured acromegaly (n=6) as glucose-suppressed GH <0.5 µg/L, and normal age- and gender-adjusted IGF-I concentration without medical treatment.

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None of the patients had hemodynamic instability, previous myocardial infarction, thyreotoxicosis, rheumatic fever, endocarditis, or connective tissue disease. None of the female patients became pregnant during the study period.

The local institutional ethics committee approved the study, and written informed consent was obtained from all subjects.

Echocardiography, Data Acquisition

The data were collected prospectively with a minimal duration of 1.5 years on the first available occasion at the outpatient clinic.

Echocardiography was performed in the patients in the left lateral decubitus position using a commercially available system (Vingmed Vivid-7, General Electric – Vingmed, Milwaukee, WI, USA). Standard parasternal (long- and short-axis) and apical views (2-, 4-, and 5-chamber) were obtained. Standard continuous-wave and pulsed-wave Doppler examinations were performed. M-mode images were obtained from the parasternal long-axis views for quantitative assessment of left ventricular (LV) dimensions (Inter-Ventricular Septum Thickness (IVST), Posterior Wall Thickness (PWT), LV End-Diastolic Diameter (LVEDD), LV End-Systolic Diameter (LVESD)), Fractional Shortening (FS) and LV Ejection Fraction (LVEF) (7).

LV mass (LVM) was calculated by the cube formula, and using the correction formula proposed by Devereux, et al. (8): $0.8 \times \{1.04\ [(LVEDD + PWT + IVST)^3 - LVEDD^3]\} + 0.6$. LVM indexation (LVMi) was corrected for body height (9). LV hypertrophy (LVH) was defined as a LVMi above 49.2 g/m$^{2.7}$ for men and 46.7 g/m$^{2.7}$ for women (9).

The severity of valvular regurgitation was assessed by two independent expert readers blinded to the clinical data on a qualitative scale of trace, mild, moderate, or severe, using previously described methods (10;11).

Hormone Assays

GH concentrations were quantitated using a sensitive time-resolved immunofluorescent assay (Wallac Oy, Turku, Finland), specific for 22 kDa GH protein. The detection limit was 0.012 µg/L. Inter-assay coefficients of variation were 8.4-1.6% in the GH-range 0.1-18 µg/L. Total serum IGF-1 concentration was determined by radioimmunoassay (RIA) after extraction and purification on ODS-silica columns (Incstar corp., Stillwater, MN, USA). The intra- and inter-assay coefficients of variation were less than 11%. The detection limit was 1.5 nmol/l. Age- and gender-adjusted IGF-I data was determined in the same laboratory. IGF-1 was expressed as a standard deviation (SD) score from age- and gender-related normal levels.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows, version 12.0 (SPSS Inc. Chicago, Illinois, USA). Results are expressed as the mean ± standard error of the mean (SEM), unless specified otherwise. Paired samples t-tests were used to assess the difference in left ventricular measurements

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at baseline and at follow-up. Independent samples t-tests were used to compare baseline values, follow-up values, and the difference in baseline and follow-up values between the two groups. Non-parametric related samples test of McNemar was used to assess the difference in fractions at baseline and follow-up. Chi-square tests were used to assess the difference in fractions between the study groups. A P-value <0.05 was considered to represent a significant difference.

RESULTS

Clinical Characteristics

The interval between the two study occasions was 1.9 years, range 1.5 to 3.0 years. Mean GH concentration and IGF-I SD scores were significantly higher in active patients, compared to inactive patients, both at baseline and at follow-up (see Table 1 for details). The activity of acromegaly decreased during follow-up in the patients with active acromegaly, reflected by a significant decrease of GH and IGF-1 concentrations at the end of follow-up. Six of the 18 patients, who were characterized as having active acromegaly at baseline, were adequately controlled at the end of follow-up. The mean duration of adequate control of acromegaly prior

Table 2/1: Clinical characteristics at baseline and follow-up.

		Active acromegaly (n=18)	Inactive acromegaly (n=19)	P-values
Age (yrs)		52.8 ± 3.8	54.8 ± 3.1	0.689
Gender (male/ female)		8/ 10	7/ 12	0.638
Follow-up duration (yrs)		2.0 ± 0.1	1.8 ± 0.1	0.247
IGF-I (SD scores)	Baseline	8.3 ± 1.9	0.8 ± 0.4	<0.001
	Follow-up	2.9 ± 0.5*	1.0 ± 0.3	0.006
GH (mU/l)	Baseline	19.0 ± 4.9	2.7 ± 0.6	0.004
	Follow-up	5.8 ± 1.4**	2.0 ± 0.5	0.009
Weight (kg)	Baseline	87.4 ± 4.0	85.9 ± 4.2	0.799
	Follow-up	85.2 ± 3.8	86.1 ± 3.9	0.875
BMI (kg/m^2)	Baseline	27.9 ± 1.0	27.7 ± 1.0	0.898
	Follow-up	28.3 ± 1.2	28.1 ± 1.0	0.879
Systolic blood pressure (mmHg)	Baseline	143.8 ± 6.3	144.7 ± 4.3	0.905
	Follow-up	132.8 ± 3.0	134.2 ± 3.7***	0.765
Diastolic blood pressure (mmHg)	Baseline	83.6 ± 2.2	84.9 ± 1.5	0.616
	Follow-up	86.4 ± 2.2	83.5 ± 1.9	0.326

Values are expressed as mean ± SEM. Within the two groups, parameters are compared between baseline and follow-up with paired samples t-tests. The two groups are compared with independent samples t-tests or chi-square tests when appropriate. BMI Body Mass Index. *IGF-I SD scores significantly decreased within active patients (P<0.001). **GH significantly decreased within active patients (P=0.017). ***Systolic blood pressure significantly decreased within inactive patients during follow-up (P=0.007).

to the first echocardiography in patients with inactive acromegaly at study entry was 7.6 years, range 0.8 to 22.7 years.

Left Ventricular Diameters and Systolic Function

At baseline, systolic function was significantly lower in patients with active acromegaly (Table 2). In addition, IVST was significantly higher in patients with active acromegaly compared to patients with inactive acromegaly. LVH was present in 61% of the active patients and in 32% of the inactive patients. This was not significantly different. Left ventricular diameters and systolic function remained unchanged during follow-up in active as well as inactive patients, except for a minimal decrease in LVEF, which was not clinically relevant. There were no differences in the difference between baseline and follow-up between active and inactive patients.

Table 2/2: Left ventricular measurements and systolic function.

		Active acromegaly (n=18)	Inactive acromegaly (n=19)	P-values	Reference values (9;21)
LVEDD (mm)	Baseline	51.1 ± 1.3	51.1 ± 2.0	0.981	40-59
	Follow-up	51.3 ± 1.1	51.3 ± 1.3	0.982	
LVESD (mm)	Baseline	33.9 ± 1.4	33.4 ± 1.5	0.805	26-40
	Follow-up	31.9 ± 1.4	32.6 ± 1.2	0.707	
FS (%)	Baseline	32.8 ± 1.7	36.6 ± 1.3	0.088	26-45
	Follow-up	37.8 ± 2.1	36.9 ± 1.5	0.713	
LVEF (%)	Baseline	62.3 ± 2.5	71.9 ± 2.0	0.005	49-79
	Follow-up	63.3 ± 4.2	65.9 ± 2.0*	0.562	
IVST (mm)	Baseline	12.6 ± 0.9	9.7 ± 0.5	0.011	<13
	Follow-up	11.3 ± 0.8	9.7 ± 0.4	0.066	
PWT (mm)	Baseline	10.3 ± 0.5	9.6 ± 0.4	0.326	<13
	Follow-up	8.6 ± 0.9	9.1 ± 0.2	0.653	
LVMi (g/ $m^{2.7}$)	Baseline	53.8 ± 6.0	42.1 ± 3.9	0.106	49.2 men/ 46.7 women
	Follow-up	45.2 ± 5.2	40.3 ± 3.1	0.418	
LVH (n (%))	Baseline	11 (61)	6 (32)	0.072	
	Follow-up	8 (44)	6 (32)	0.420	

Values are expressed as mean ± SEM. Within the two groups, parameters are compared between baseline and follow-up with paired samples t-tests. The two groups are compared with independent samples t-tests or chi-square tests when appropriate. Reference values are obtained from Ilercil *et al.* (21) and Vitale *et al.* (9). LVEDD Left Ventricular End-Diastolic Diameter; LVESD Left Ventricular End-Systolic Diameter, FS Fractional shortening, LVEF Left Ventricular Ejection Fraction, IVST Inter-Ventricular Septum Thickness, PWT Posterior Wall Thickness, LVMi Left Ventricular Mass Index, LVH Left Ventricular Hypertrophy. *LVEF significantly decreased within inactive patients during follow-up (P=0.038).

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Prevalence of valvular regurgitation in the total cohort

At baseline, valvular regurgitation at mitral and aortic sites combined was present in 17 of the 37 patients (46%) and during follow-up in 24 patients (67%, p=0.008 vs. baseline, Table 3). The prevalence of mitral regurgitation significantly increased in the total cohort from 32% at baseline to 60% at follow-up (p=0.002), but the prevalence of aortic regurgitation remained unchanged (27% at baseline and 31% at follow-up, NS).

Table 2/3: Prevalence of mitral and aortic regurgitation in patients with acromegaly at baseline and follow-up.

		None	Trace	Mild	Moderate	Severe
Aortic valve (n (%))	Baseline	27 (73)	4 (11)	5 (14)	0	1* (3)
	Follow-up	25 (69)	4 (11)	7 (19)	0	0
Mitral valve (n (%))	Baseline	25 (68)	8 (22)	4 (11)	0	0
	Follow-up	15 (41)	12 (32)	10 (27)	0	0

Data are presented as number (percentages) of patients. *Valvular replacement surgery after first cardiac assessment.

Influence of active vs. inactive acromegaly on valvular regurgitation

In patients with active acromegaly, the percentage of valvular regurgitation at mitral and aortic sites combined increased significantly (56% at baseline to 88% at follow-up, p=0.031), whereas there were no significant changes in patients with inactive disease (26% at baseline vs. 47% at follow-up, p=0.500). The percentage of active acromegalic patients with mitral regurgitation increased during follow-up from 39% at baseline to 78% (p=0.016), whereas there was no change in inactive acromegalic patients (26% at baseline vs. 42% at follow-up, p=0.250) and no

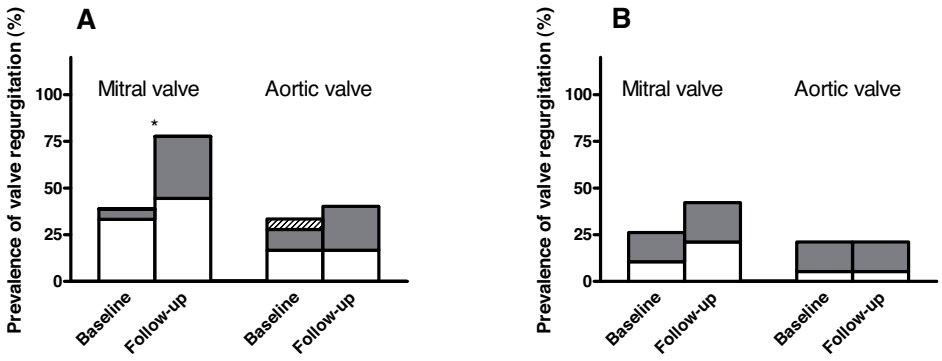

Figure 2/1: The prevalence of mitral or aortic regurgitation at baseline and at follow-up in patients with active and inactive acromegaly.

A: Active acromegaly (n=18); B: Inactive acromegaly (n=19); White bars denote trace regurgitation, gray bars denote mild regurgitation, hatched bars denote severe regurgititation (this patient had valve replacement surgery during follow-up).

*During follow-up the prevalence of trace and mitral regurgitation significantly increases in patients with active acromegaly (P=0.016). The prevalence of mitral regurgitation in patients with inactive disease was 26% at baseline vs. 42% at follow-up, P=0.250.

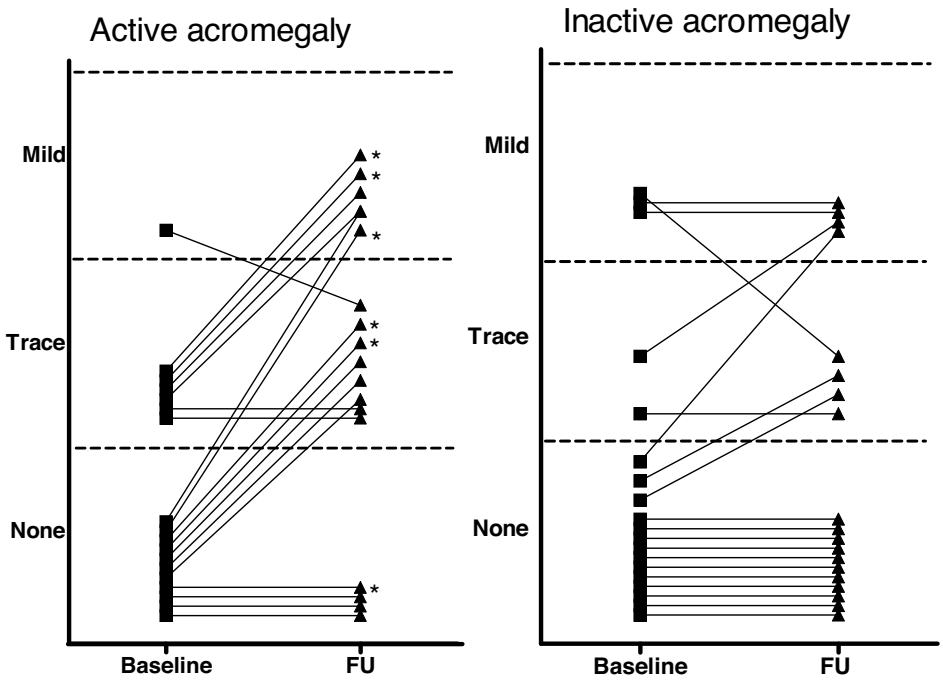

Figure 2/2: Individual course of mitral regurgitation among patients with active acromegaly (left panel) and patients with inactive acromegaly at study entry (right panel). *Patients who were classified as active acromegaly at baseline and were adequately controlled at follow-up (FU).

change in the prevalence of aortic valve regurgitation in both active and inactive patients (Figure 1 and 2). Therefore, the increase in valvular regurgitation in the total cohort of acromegalic patients was explained by an increase in trace and mild mitral valve regurgitation in patients with active acromegaly. In addition, we found no significant difference in the prevalence of mitral/ aortic/ or any valvular regurgitation (mitral and aortic sites combined) between patients with left ventricular hypertrophy and patients without left ventricular hypertrophy, neither in the total cohort, nor when active and inactive patients were analyzed separately.

DISCUSSION

This observational follow-up study demonstrates, that the prevalence of trace and mild mitral valvular regurgitation increased in patients with active acromegaly. These new data reinforce the concept, that acromegaly induces regurgitant valvular disease (5;6). Conversely, adequate control of GH excess is associated with stable valvular function, at least during the follow-up of our study.

The increase in prevalence in valvular regurgitation in active acromegaly in this study was explained by mitral valve involvement, whereas there was no change in aortic valvular regurgitation. This finding is in line with the observed prevalence of mitral and aortic regurgitation in the Framingham heart study, in which mitral regurgitation was more prevalent than aortic regurgitation (12). Prevalences of more than or equal to mild severity mitral regurgitation and more than or equal to trace severity aortic regurgitation were found in approximately 19% and 11%, respectively. In our age- and sex matched controls the prevalences of any aortic regurgitation and any mitral regurgitation were 7% and 32%, respectively (5). One of the major determinants of valvular regurgitation in the general population proved to be increasing age (12). Previously, we could not confirm a significant influence of age in this specific group of acromegalic patients (5). Why the increase in regurgitation in our patients was only observed for the mitral valve might be related to differences in the intrinsic vulnerability between the aortic and mitral valve to exogenous stimuli that promote valvular degenerative changes. For instance, it has been documented that mitral regurgitation, but not aortic regurgitation, is associated with systemic hypertension (12). In addition, it has been postulated that increased afterload may play an important role in the development of minor degrees of mitral regurgitation (12). Given the myxomatous degeneration found in the valves that were removed from several of our acromegalic patients during valvular replacement surgery (5), we postulate that persistent long-term exposure to GH excess predisposes to accelerated degenerative valvular changes. It is also of note that the myxomatous degeneration in acromegaly resembles that found in connective tissue diseases, conditions that are also associated with irreversible valvular disease (13).

Valve regurgitation was asymptomatic except for one patient and varied from only of trace to mild severity. Therefore, the clinical relevance of our findings might be questioned. In this regard recent findings of the impact of asymptomatic valvular regurgitation by Enriquez-Sarano et al. are relevant (14). They found that in the general population, the severity of mitral regurgitation was a powerful predictor of clinical outcome in terms of death from any cause and death from cardiac disease (14). Given the strong correlation between acromegaly and cardiovascular morbidity, at least in active acromegaly (2), asymptomatic valvular regurgitation may contribute to the increased cardiovascular risk profile of these patients. It should be noted that the duration of follow-up in our current study was relatively short and that a longer duration of follow-up could have resulted in more severe valvular changes, because the development of valvular involvement is correlated with the duration of active disease (5).

At the end of the study, several patients of the group with clinically active acromegaly finally had normal GH and IGF-I concentrations, but, nevertheless, in this group the progression of valvular disease took place. At present, it is not known how long disease activity must be controlled to prevent further deterioration of valvular disease. These observations indicate that the duration might be much longer from seen for improvement of myocardial involvement. Myocardial involment is a well recognised complication of acromegaly (2) and seems to be

related to the direct effects of GH and/or IGF-I on the myocardium (15). GH excess leads to the development of myocardial hypertrophy with interstitial fibrosis, resulting in diastolic dysfunction with impaired systolic function during exercise. Reversal of GH and IGF-I excess by surgical removal of the GH secreting pituitary tumour and/or medication attenuates or even reverses abnormal LV measurements and function in acromegalic cardiomyopathy (16;17). Octreotide treatment is known to improve LV function and decrease LV wall thickness in acromegaly (17). These beneficial changes become apparent within 6 months after treatment. The absence of improvement in left ventricular parameters in patients with inactive acromegaly is most likely explained by the fact, that these patients were adequately treated for many years prior to the first echocardiography. The LVEF in inactive patients decreased, which was clinically irrelevant, and within the reference values.

The lack of any effect of persistent inactive disease on valvular regurgitation could suggest that myocardial changes induced by previous acromegaly are partly irreversible. We could not identify any evident differences in clinical parameters between inactive acromegalic patients, who had progression of valvular regurgitation during follow-up, and the other inactive acromegalic patients. However, since the present study is an observational study rather than an intervention study, reversibility of myocardial abnormalities was not studied. The left ventricular indices are presented mainly to demonstrate that the observed changes in valvular heart disease are not caused by changes in left ventricular diameters or function, but probably due to the effects of GH and IGF-I on connective tissue (18-20).

In conclusion, we demonstrated that the prevalence of regurgitant valvular heart disease increases during follow up of patients with active acromegaly. Patients with acromegaly require adequate cardiac evaluation to establish the extent of valvular involvement in acromegalic disease and to install appropriate cardiac monitoring and care.

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