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Chapter 4

Increased Prevalence of Regurgitant Valvular Heart Disease in Acromegaly

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Abstract

Cardiac involvement is common in acromegaly, but the prevalence of valvular abnormalities in patients with acromegaly has not been documented, and was topic of the current study.

In a prospective study design, 40 consecutive patients with acromegaly and 120 control subjects (matched for age, sex, hypertension, and left ventricular systolic function) were studied. All patients and controls were evaluated using conventional 2D and Doppler echocardiography. Significant valve disease was more prevalent in acromegalics compared to controls: 22% vs 6.7% ($p=0.005$). Aortic valve regurgitation (more than or equal to trace severity) was present in 30% of patients vs 7% in controls ($p<0.001$), mitral regurgitation (more than or equal to moderate severity was absent in controls, but present in 5% of acromegalics ($p=0.014$ vs controls). Binary logistic regression analysis showed a significant impact only for disease duration on valvular disease, with an odds ratio of 1.19 (CI 1.028 – 1.376; $p=0.019$).

Acromegaly is associated with an increased prevalence of regurgitant valvular heart disease. This is dependent on the duration of exposure to increased growth hormone concentrations, with a 19% increase in odds per year. This increased prevalence of occult valvular disease implicates that these patients require appropriate follow-up care and monitoring, especially those with inadequate control of GH overproduction.

Introduction

Acromegaly is associated with increased cardiac morbidity and mortality. Recognized manifestations of cardiac disease in this population include chronic heart failure (CHF) due to either global systolic dysfunction (cardiomyopathy) or to diastolic dysfunction with preserved systolic function. The pathophysiology of these cardiac complications of acromegaly is incompletely understood. It has been hypothesized that abnormal extracellular matrix regulation by overproduction of growth hormone (GH) or IGF-1 in patients with acromegaly may contribute to both systolic and diastolic myocardial dysfunction (1). In addition, GH can increase circulating pro-inflammatory cytokine levels, like IL-1-beta and TNF-alpha (2). These cytokines, in turn, increase gene expression of matrix metalloproteinases (MMPs), that are capable of altering the composition of the extracellular matrix (3). These abnormalities in matrix regulation are associated with cardiac chamber dilation and reduced myocardial tensile strength (4). Abnormalities in matrix regulation have also been implicated in the pathogenesis of aortic and mitral valve disease (5-7) the latter of which is manifest as thickened and redundant valves which are incompetent and have an appearance of myxoid degeneration on pathology.

We hypothesized that patients with acromegaly, in whom GH and IGF-1 are pathologically elevated, have an increased incidence of clinically relevant aortic and mitral valve disease. There are anecdotal reports of aortic or mitral valve operations performed in patients with acromegaly that support this concept (8,9). However, the prevalence of valvular abnormalities in patients with acromegaly has not been documented. Therefore, we prospectively evaluated the prevalence of valvular abnormalities in patients with acromegaly and no prior history of cardiac disease.

Methods

Patients and controls

In a prospective study design, 40 patients (19 male and 21 female) with acromegaly were studied. The median age of the patients was 57 years (range 20-83 yrs). Nine patients were untreated (de novo patients), and 31 patients were treated either by transphenoidal surgery (n=23) or by primary medical treatment (n=8) (Table 1). The diagnosis of acromegaly was based on the characteristic clinical features of acromegaly and confirmed by insufficient suppression of GH concentration during a glucose tolerance test and the presence of a pituitary adenoma on radiological imaging. Disease activity was assessed as follows: Patients were classified as having active disease if they had mean fasting GH concentration (measured every 30 min for 3 hours) >5 mU/L and elevated age- and sex adjusted IGF-1 concentrations. Patients were classified as having inactive disease if mean GH concentration during fasting 3h profile were <5 mU/L and IGF-1 concentrations were normal. A total of 18 patients were classified as having active disease (nine de novo patients and nine patients treated with depot octreotide acetate), and 22 patients as having inactive disease (eight cured patients and fourteen patients on depot octreotide acetate). Patients with hemodynamic instability, or a prior history of myocardial infarction, thyrotoxicosis, rheumatic fever, endocarditis, anorexigen use, or other connective tissue disease were excluded from the study. Also, in female patients of childbearing age pregnancy was excluded. None of the patients appeared to be pregnant in the 9 months following echocardiography. The duration of disease was defined by the onset of clinical symptoms related to GH excess (carpal tunnel syndrome, sleep apnea, and arthralgias), and by careful comparison of old photographs. The end of disease duration was defined as the time of successful treatment.

Acromegalic patients are rare, whereas controls with similar age/sex/comorbidities are not, hence we selected a larger control group. The acromegaly patients were collected first (with history and examinations) and 120 appropriate controls were selected based on age, sex, hypertension, left ventricular systolic function, based on a database with

this info. We controlled for systolic function to eliminate the possibility of getting a lot of patients with mitral regurgitation on the basis of left ventricular enlargement (incomplete closure). Patients were excluded if they were sent for echocardiatic evaluation of known valvular disease, murmur, congestive heart failure, or cardiac transplant evaluation. Accordingly, most of the control patients were referred for either atypical chest pain, palpitations, or syncope without murmur. The study was approved by the local institutional ethics committees, and written informed consent was obtained from all subjects.

Echocardiography, Data Acquisition

Patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed system FiVe, General Electric – Vingmed, Milwaukee, WI, USA). B-mode 2-D images were obtained with transmission frequencies of xx-3.5 MHz in the parasternal (standard long- and short-axis) and apical views (2-, 4-, and 5-chamber images). Color Doppler echocardiography was performed in all views after optimizing gain and Nyquist limit. Standard continuous-wave and pulse-wave Doppler examinations were performed. M-mode images were obtained from the parasternal long-axis views for quantitative assessment of LV dimensions, fractional shortening and left ventricular ejection fraction (10). When tricuspid regurgitation was present, pulmonary artery pressure was estimated using the modified Bernoulli equation. The severity of valvular regurgitant was determined by two independent expert readers blinded to the clinical data on a qualitative scale of trace, mild, moderate or severe, using previously described methods (11,12). Significant valvular disease was determined using the FDA case definition: mild or greater aortic regurgitation or mitral regurgitation equal or more than moderate severity (13).

Hormone assays

GH concentrations were quantitated in duplicate using a sensitive time-resolved immunofluorescent assay (Wallac Oy, Turku, Finland), specific for 22 kDA GH protein. The detection limit was 0.03 mU/l (0.01 ig/L). Intra-assay coefficients of variation were 1.6-8.4% in the GH-range 0.1-

18 $\mu\text{g/L}$ (0.26-47 mU/L). The total serum IGF-1 concentration was determined by radioimmunoassay (RIA) after extraction and purification on ODS-silica columns (Incstar corp., Stillwater, MN, USA). The inter-assay coefficient of variation was less than 11%. The detection limit was 1.5 nmol/L . Age related normal data were determined in the same laboratory. IGF-1 was also expressed as a standard deviation score from age-related normal levels.

Statistical analysis

Student's *t*-test was used for continuous variables. The Chi-square test and the Cochran-Mantel test were used to compare continuous and categorical data to detect trends. Binary logistic regression stepwise was performed to explore possible determinants of valvular disease. SPSS software version 10.0 (Inc, Chicago, USA) was used. Differences were considered statistically significant at the $p < 0.05$ level.

Table 1. Patients Characteristics

	Patients (n=40)
Age (yrs)	59 ± 13.7
Sex (m/f)	19/21
BMI	28.2 ± 3.3
Cholesterol	5.65 ± 1.1
HDL	1.6 ± 0.39
Triglycerides	1.3 ± 0.52
HbA1c	5.59 ± 0.9
Hypertension	11 (27.5%)
Disease duration (yrs)	12.2 (1-46)
Previous transsphenoidal surgery	23
Active disease	
De novo	9
<i>Active</i>	9
Inactive disease	
Well- controlled	14
<i>Cured</i>	8
Octreotide treatment	23 (57%)
GH at presentation	$91.7 \pm 126.7 \text{ mU/L}$ (range: 5-470)
IGF-1 at presentation	$70.6 \pm 33.8 \text{ nmol/L}$ (range: 28-162)

Data presented as mean $\pm$ SD

Results

Left ventricular systolic function and dimensions in acromegalic patients were within the normal range (see Table 2). However, ten patients (25%) had left ventricular hypertrophy, defined by interventricular septum thickness (IVST) above 12 mm (n=9) and/or a posterior wall thickness (PWT) (n=6) above 12 mm. Their corrected Left Ventricular Mass index (LVMI) was above 110 gr/m² (for women) and 125 gr/m² (for men). Five of these ten patients had significant valve disease. Six patients had slightly increased LV dimensions (left ventricular end diastolic volume below 59 mm and < 32 mm, corrected for height, five of whom had normal left ventricular mass. (four of the six patients had significant valve disease).

Valvular stenosis was neither seen in patients with acromegaly, nor in controls. Any valve disease was seen in 50% of patients and in 50% of controls. Significant valve disease (by FDA criteria) was seen in 22% (9/40) of patients vs 6.7% (8/120) in controls (p=0.005) (or even only 4% (5/120) in control subjects if only mitral and aortic valve were analyzed). Three patients were subsequently operated, two for severe mitral valve regurgitation, and one for severe aortic valve regurgitation. The three patients, that underwent valve surgery, presented with following symptoms prior to echocardiography. The first patient was diagnosed with a systolic and diastolic murmur on preoperative

Table 2. Left ventricular measurements in acromegalic patients

	All patients	Normal values
LVEDD (mm)	53±8	40-59
LVESD (mm)	35±9	26-42
IVST (mm)	11±3	< 13
IVST >12 mm	n=9	
PST (mm)	10±2	< 13
PST >12 mm	n=6	
FS (%)	35±8	26-45
LVEF (%)	70±11	49-79

Data presented as mean ± SD. Normal values derived from : J Am Soc Echocardiography 2001;14:601-11 (ref no 18)
 LVEDD:left ventricular enddiastolic diameter;LVESD:left ventricular endsystolic diameter; IVST: inter ventricular septum thickness; PWT: posterior wall thickness; FS: fractional shortening; LVEF: left ventricular ejection fraction

screening for a knee operation. The second patient had palpitations during physical exercise as a presenting symptom. The third patient did not experience any symptoms, although he had hypertension.

Prevalence of regurgitation (Table 3)

Aortic valve regurgitation was present in 30% (12/40) of patients vs 7% (8/120) in controls ($p<0.001$). These differences were significant for all grades of severity of regurgitation detected. Significant aortic valve regurgitation (by FDA criteria) was present in 20% (8/40) of patients vs 4% (5/120) in controls ($p=0.002$).

Mitral valve regurgitation was detectable in 35% (14/40) of the patients vs 32% (39/120) of control subjects (NS). However, pathological mitral regurgitation (moderate or severe according to the FDA criteria) was absent in controls, but present in 5% (2/40) of acromegalics ($p=0.014$, vs controls).

Table 3. Valvular regurgitation in acromegalic patients (n=40) compared to controls (n=120).

Valves		None % (n)	Trace % (n)	Mild % (n)	Moderate % (n)	Severe % (n)
Aortic*	<i>Patients</i>	70 (28)	10 (4)	17.5 (7)*	0	2.5 (1) *
	<i>Controls</i>	93 (112)	3 (3)	4 (5)	0	0
Mitral	<i>Patients</i>	65 (26)	20 (8)	10 (4)	0	5 (2) †
	<i>Controls</i>	68 (81)	18 (22)	14 (17)	0	0
Tricuspid	<i>Patients</i>	72 (33)	20 (8)	8 (3)	0	0
	<i>Controls</i>	50 (60)	27 (32)	20 (24)	3 (3)	0

* $P=0.002$ patients vs controls

† $P=0.014$ patients vs controls

Tricuspid valve regurgitation was detectable in 28% (11/40) of the patients vs 50% (60/120) of control subjects. However, pathological tricuspid regurgitation (moderate or severe according to the FDA criteria) was absent in all patients and present in only 3% (3/120) of control subjects. This difference was not significantly different.

Valvular regurgitation of one valve was present in ten patients, valvular regurgitation of two valves in two patients, and valvular regurgitation of three valves in two patients.

Prevalence rates of valvular abnormalities were similar between active and inactive patients.

Determinants of valvular disease

Figure 1 describes the impact of disease duration on valvular disease in the acromegalic patients. Binary logistic regression analysis showed a significant impact of disease duration on valvular disease, odds ratio 1.19 (CI 1.028 – 1.376); i.e. every additional year of disease would result in a 19% increase in odds per year.

To explore other possible determinants of valvular disease, binary logistic regression analysis with a stepwise approach was performed. The following parameters were analyzed: IGF-1 and GH concentrations at time of diagnosis, age, active- vs inactive disease, (previous) treatment with octreotide, and the presence of hypertension. No significant correlations were found for any of the above mentioned parameters.

Discussion

This study clearly demonstrates that in patients with acromegaly, valvular abnormalities are more prevalent than in control subjects, who were individually matched for left ventricular function, age, sex, and the presence of hypertension. Moreover, we are the first to show that the prevalence of valvular disease in acromegaly proves to be highly significantly correlated to the duration of the disease.

In this study, we compared echocardiographic data in patients with acromegaly with active or inactive disease to a control data base. Matched data base analysis is necessary due to the relatively high prevalence of mild valvular abnormalities in the general population, which tends to increase with age. Studies using 2D color doppler echocardiography with a semiquantitative methods for estimating the severity of regurgitation from trace to severe, have demonstrated that the population-based prevalence of minimal or mild mitral and tricuspid valve regurgitation was quite high (58-77%), whereas aortic valve regurgitation was much less prevalent (14,15). Accordingly, the United States Food and Drug Administration (FDA) has defined pathological regurgitation of the mitral and tricuspid valve as more than or equal to moderate severity, and pathological regurgitation of the aortic valve as more than or equal to mild severity. However, in the normal offspring in the Framingham Heart Study (14), trace severity for mitral and tricuspid valve was present in 75% of the subjects and independent on age, whereas trace aortic regurgitation was only present in about 5% of subjects and strongly dependent on age (from about 2% at the age of 26-39 years to about 10% at the age of 70-83 years). Therefore, it has been postulated, that the FDA's criteria for aortic regurgitation may be too narrow, and the case definition for pathologic regurgitation may need to be modified or made age specific (15). In our study, we therefore individually matched each acromegalic patient for age, sex and the presence of hypertension, to three non acromegalic control subjects. We observed prevalence rates of any and significant valvular regurgitation in these 120 control subjects comparable to those reported in the normal offspring in the Framingham Heart Study. Aortic

regurgitation (present in 13% of men and 8% of women in the Framingham Heart Study) was present in 7% of our control subjects, vs in 30% of our patients with acromegaly. However, the abnormalities detected were predominantly mitral regurgitation of trace severity. This is due to the temporal/spatial high resolution of the echo equipment available (GE vivid 7, Vingmed system FiVe).

The pathogenesis of myxomatous heart valve degeneration remains uncertain. Rabkin and co-workers (6), proposed a model in which activation of interstitial cardiac valve cells leads to the release of proteolytic enzymes, phenotypic modulation, and proliferation. Subsequently, degradation of collagen, elastin fragmentation, and glycosaminoglycans accumulation produces extracellular matrix remodeling, and characteristic leaflet myxomatous thickening and redundancy. However, the primary stimulus for activation of these resting fibroblast-like interstitial cells remains to be elucidated, but mechanical stress and genetic abnormalities are proposed to play a key role. In our three patients who underwent valve replacement surgery, similar

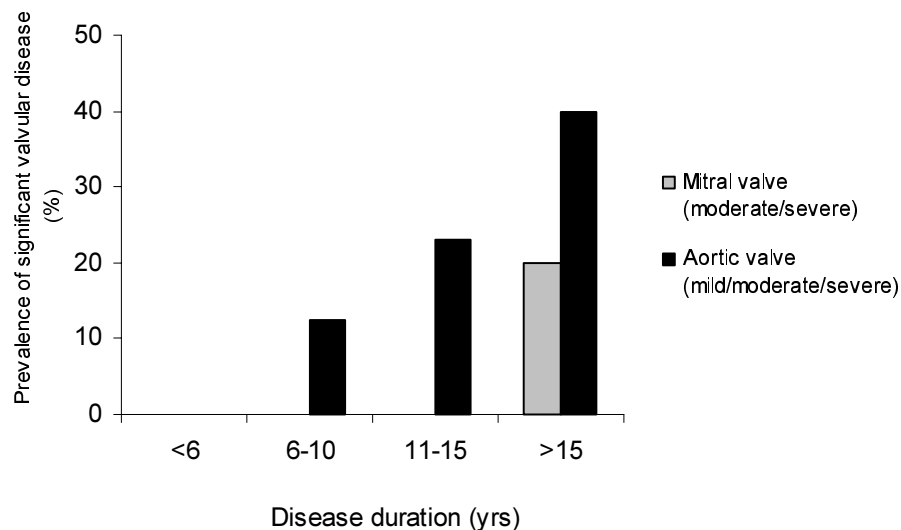


Figure 1: The impact of disease duration on the prevalence of significant valvular disease

pathological changes of myxomatous degeneration were observed (Figure 2). It is likely that direct or indirect effects of overproduction of GH are the causes for the observed valvular incompetence, for the following reasons. First, GH increases gene expression of the matrix metalloproteinases (MMPs)(16), resulting in abnormal matrix regulation. Second, recent data indicate that pro-inflammatory cytokine levels are increased in acromegalic patients with active disease (17). These cytokines, in turn, can also increase gene expression of MMPs, resulting in abnormal matrix regulation. Finally, the prevalence of valvular regurgitation observed in our acromegalic patients proved to be highly significantly correlated to the duration of the disease. Whereas pathological valvular regurgitation was absent in patients with an estimated disease duration of less than 6 years, the prevalence of aortic valve regurgitation (more than or equal to mild severity), increased from 12.5% for patients with a disease duration of 6 to 10 years, to 40% in patients with disease duration of more than 16 years. Similarly, prevalence of mitral valve regurgitation (more than or equal to moderate severity) was absent in controls, but present in 20% of acromegalic patients with disease duration of more than 16 years. Whether the patients had active disease or not at the time of evaluation did not influence these prevalence rates. From a pathophysiological point of view this is very interesting, since the valvular damage is apparently irreversible (in contrast to the already published regression of LVH in successfully treated patients). This is also in accordance with the recently published study by Colao, et al. who reports an unexpectedly high prevalence of valve abnormalities in patients successfully cured of acromegaly (19). Hence, chronic exposure to increased GH or IGF-1 production predisposes for myxomatous degeneration, with a calculated increase in odds in our study of 19% for the development of valvular disease for every additional year of exposure to tonically elevated growth hormone concentrations. Because the onset of GH overproduction is gradual, there is in general a long patient delay before the diagnosis of acromegaly is made. Therefore, it can be argued that an accurate assessment of disease duration is cumbersome. Before the onset of clinical symptoms, careful comparison of old photographs reveal (often

subtle, but clear) changes of the face. This retrospective evaluation of the combination of the onset of clinical symptoms and comparison of old photographs proved to be reproducible for estimating disease duration and to find significant associations of this estimated disease duration with mortality (20), as well as with left ventricular hypertrophy and cardiac performance (21). However, this way of assessing disease duration will still lead to inaccuracies. Therefore, we decided to present the impact of disease duration of acromegaly on valvular disease also by stepwise increasing disease duration by very large intervals of 5 years. Highly significant increases in the prevalence of valvular disease were found between every five year interval and the preceding five years (figure 1). Eventhough there remain uncertanties with respect to the exact start of acromegaly, this analysis strongly support our notion that the prevalence of valvular heart disease is dependent on disease duration.

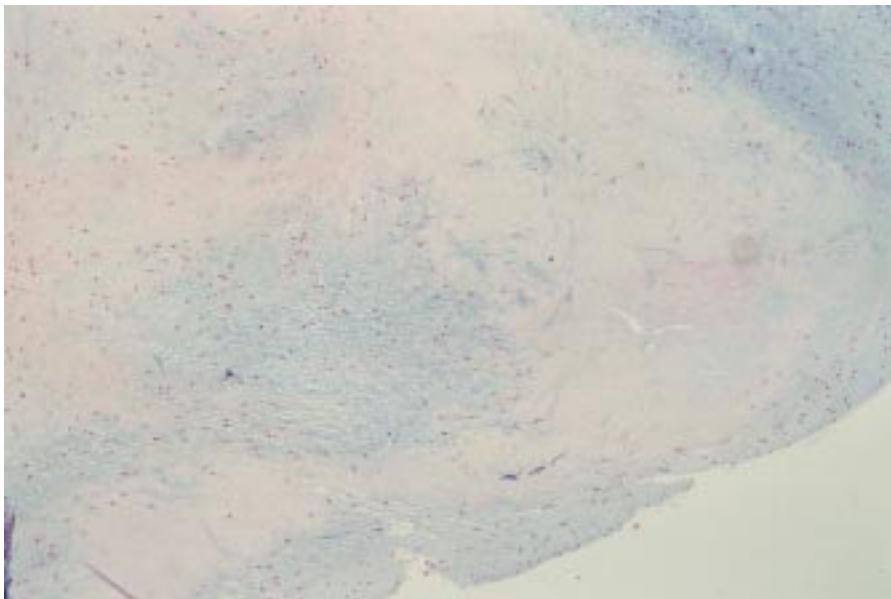


Figure 2: Mitral valve showing degenerative changes such as mucoid alteration of the preexistent collagenous tissue as indicated by the bleuish staining (Alcian blue staining, magnification x 100)

It is interesting to note that all patients in whom valvular abnormalities were detected, had normal LV function and that 85% (17/20) of these patients also had normal dimensions. This suggests that valvular disease duration was brief for most patients. The discrepancy between the relative lack of cardiomyopathic responses in most patients in our study compared to the recently published study of Colao et al.(19) is striking, even though we found similar rates of regurgitant valve disease. However, considering the fact that 57% of our patients had been adequately controlled for a long time by octreotide therapy, and that they had similar prevalence rates of regurgitant valve disease as those without octreotide treatment, the following notion emerges. Octreotide is known to reverse the development of LVH (22). However, apparently, this was not reflected in a lower rate of regurgitant valve disease. In line with this notion we found fibrinoid changes in the valves that were removed. These changes are in other diseases associated with irreversible valve disease. Based on the comparison of the data of Colao, et al. (19) and our study, we hypothesize that regurgitant valvular disease in acromegaly may be less amenable to therapeutic intervention aimed at reducing excessive GH secretion than myocardial complications of acromegaly.

In conclusion, we are the first to report that acromegaly is associated with an increased prevalence of regurgitant valvular heart disease, which is dependent of the duration of exposure to increased growth hormone concentrations, and which is not associated with impaired left ventricular function nor hypertension. This increased likelihood of valve disease may impact the cardiac surveillance of patients with acromegaly and could provide us more insight on the basic pathophysiological interactions of growth hormone with connective tissues. The increased prevalence of occult valve disease implicates that these patients require appropriate follow-up care and monitoring, especially those with inadequate control of GH overproduction. Moreover, antibiotic prophylaxis for any non-sterile procedures may be required.

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