CARDIOVASCULAR COMPLICATIONS OF ACROMEGALY

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Abstract

Acromegaly is associated with increased mortality and decreased life expectancy. Cardiovascular disease is the principal cause of premature mortality in patients with acromegaly, accounting for about 60% of deaths. GH and/or IGF-I exert direct cardiac effects: enhance cardiac contractility, stimulate cardiomyocyte growth, influence calcium influx in cardiomyocytes. Cardiac remodelling is influenced by hypertension and insulin resistance. Among cardiovascular risk factors arterial hypertension, reported in 35% of patients with acromegaly, ranks among most important negative prognostic factors for mortality. Hypertension plays significant role in the development of cardiac hypertrophy, especially in older acromegalic patients and diastolic blood pressure is best predictive factor for cardiac hypertrophy. Therefore, early and aggressive hypertension treatment is essential for prognosis in acromegaly. Other important risk factors are: valvular defects, arrhythmias, endothelial dysfunction, heart failure, lipid abnormalities and coronary artery disease. Numerous studies suggest that patients with acromegaly are under threat of arrhythmias, especially those with structural heart abnormalities. Congestive heart failure as end-stage acromegalic cardiomyopathy occurs usually in older patients, with long-term uncontrolled disease and other cardiovascular and metabolic complications. Relation between acromegaly and coronary artery disease is controversial as it seems to be connected rather with classical cardiovascular risk factors than GH and IGF-I overexpression.

Key words: acromegaly, complications.

INTRODUCTION

Acromegaly is a chronic systemic disease caused by the benign pituitary adenoma secreting growth hormone (GH) in excess, which peripheral effect is mediated by insulin-like growth factor 1 (IGF-I) produced by the liver. The incidence of acromegaly is 3-5/million/year, prevalence 40-130/million, recent population studies suggest greater prevalence of acromegaly than previously thought

(1-3). Majority of patients harbour macroadenoma (≥ 10 mm) at the diagnosis, typical clinical features and presence of systemic complications (4). Transsphenoidal neurosurgery is the therapy of primary choice for most acromegaly patients, but its efficacy is limited to about 50% depending on adenoma size, its expansion and neurosurgeon's experience. In patients who remain not cured after surgery, medical therapies are applied. Among them, somatostatin analogs (SA) are the first choice adjuvant therapy, other are GH receptor antagonist (pegvisomant) or dopamine agonist (cabergoline) as monotherapy or given additionally to SA. Stereotactic radiotherapy (radiosurgery) remains an alternative option. Uncontrolled disease is associated with increased risk for cardiovascular, respiratory, metabolic and neoplastic complications and higher mortality rates than in the general population (5, 6).

Cardiovascular disease is a principal cause of premature mortality in acromegaly. Increased mortality is characterized by 1.5-2.5 times higher standardized mortality ratio, what means shorter life expectancy of approximately 10 years in not cured patients. Another important factor is a 5-10 years delay in the final diagnosis what influences the progression of the disease and development of complications. Among factors affecting mortality in acromegaly, GH concentration, hypertension and heart disease are main ones, before other like disease or symptoms duration, diabetes etc (7,8).

Both GH and IGF-I exert direct cardiac effects: enhance cardiac contractility, stimulate cardiomyocyte growth, reduce systemic vascular resistance, influence calcium ions influx and raise peak calcium ion levels in cardiomyocytes. On the other hand, cardiac remodelling is influenced by hypertension and insulin resistance. The final effect of GH action is an increase of cardiac contractility and left ventricle mass, decrease of wall stress and vascular resistance leading to the increase of cardiac performance (9).

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HYPERTENSION

Hypertension is among the most common complications of acromegaly. In meta-analysis of 2562 patients from 11 series the reported mean prevalence was 35% (ranging from 18 to 60%) (10). However, data is based mainly on office measurements and only in a few studies utilised 24-h blood pressure (BP) ambulatory recording, thus outcomes may be overestimated (11). Nonetheless, research definitely shows prevalence higher than in general population with nearly doubled hazard ratio (12). As in general population incidence of hypertension in acromegaly increases with age, but occurrence is earlier and affected subjects are nearly 10 years younger (12). Prevalence is independent of duration of the disease, but related to the extent of GH hypersecretion (10).

Being one of the most common, it is also among the most disadvantageous complication, while it has been shown to be the major independent determinant of mortality (8) and factor worsening cardiac hypertrophy and progression towards heart failure.

There are certain differences in characteristic comparing to primary hypertension. In a group of 92 hypertensive acromegalics diastolic blood pressure was significantly higher and systolic significantly lower compared to controls indicating predominantly diastolic involvement (12). Non-dipper profile is also more commonly observed with the incidence reaching nearly 50% (10) and family history of hypertension is less common (12).

These distinctive features imply different pathogenesis of hypertension secondary to acromegaly from that of primary hypertension. The biological mechanisms underlying hypertension development in this entity seem to be complex and still are not fully explicated. Both direct effects of GH and IGF-I oversecretion as well as mediated by systemic changes like insulin resistance or occurrence of sleep apnoea syndrome seem to play a vital role (10).

Sodium and water retention

Acromegaly has been long connected with increased plasma volume by water and sodium retention (13) what most probably plays a key role in hypertension development (10). The exchangeable sodium was shown to be increased in active acromegaly (14) often being greater than values found in Conn's syndrome (15), correlate with blood pressure and GH log levels and decrease after successful treatment (15).

The precise means by which GH causes antinatriuretic effect are not completely understood. It seems that it occurs mainly, if not solely, without involvement of the activation of the renin-angiotensin system. Numerous studies suggest suppression of atrial natriuretic peptide (16), yet data shows no statistically significant differences between active and controlled acromegaly (17).

Recent research favor a direct effect of GH on sodium and water reabsorption in the kidney tubule. Exact segment of nephron where GH/IGF-I axis regulates sodium reabsorption is still uncertain. Although some human metabolic studies suggested that GH affects directly epithelial sodium channel in distal tubule (16).

Renin-angiotensin-aldosterone (RAA)

Studies on influence of GH/IGF-I administration on RAA axis based on animals, normal and growth hormone deficient populations are scarce and provided conflicting results showing stimulatory (18) as well as no significant effect (19). In the studies on acromegaly plasma renin activity has been repeatedly reported to be low (10). There is also data demonstrating blunted aldosterone response to endogenous and exogenous angiotensin II with concurrent increased vascular response (rise in blood pressure) to exogenous angiotensin II (20). All of these outcomes may be consequences of sodium retention and volume expansion and indeed are found in sodium loaded normal subjects. Nevertheless, there is some research showing that the level of plasma renin seems to be lower than expected for the degree of sodium retention and aldosterone levels are neither suppressed nor related to plasma renin activity (21). Together with the fact that GH receptors on adrenal cells have been identified it raises a question about direct stimulatory effect of GH on adrenals, which due to lack of data remains unanswered.

Hyperinsulinemia

GH excess is responsible for development of insulin resistance, which further causes hyperinsulinemia. GH actions are mainly mediated by increased lipolysis and free fatty acids production causing general increase of resistance to insulin in liver and other tissues such as skeletal muscles and adipose tissue. Another pathomechanism is direct effect of GH on increase in endogenous glucose production in liver and decrease of peripheral glucose metabolism in muscles (22–24). On the other hand, its

indirect action via IGF-I may, in turn, facilitate weak insulin effects (25).

Insulin resistance and high circulating insulin levels, may increase blood pressure and induce development of hypertension in acromegaly by several mechanisms including stimulating transcellular sodium transport causing renal sodium reabsorption, increasing sympathetic activity and RAA axis, promoting vascular smooth cell growth, impairment of endothelial function and thus vasodilatation (10). In accordance with these facts blood pressure has been found higher in hyperinsulinemic patients with acromegaly (26).

Sleep apnea syndrome

Sleep apnea syndrome is a complex disease that affects various organs and systems and is observed in 20-80% of patients with acromegaly (27,28). High prevalence is an effect of direct actions of GH and IGF-I on craniofacial bones and soft tissues. The wide range of anatomical changes includes: swelling of the tongue, changes in the mucous and cartilages, increased lung volume, geometry of rib cage and reduced elasticity of lungs (27,29). This condition is generally known to predispose to hypertension and arrhythmias (30). Increase in BP is caused by multiple mechanisms including peripheral vasoconstriction induced by increased sympathetic activity provoked by periods of desaturation and re-oxygenation (31–33). Intermittent hypoxemia has been shown to activate RAA system (33,34). There is also vascular dysfunction and stimulation of systemic inflammation induced by an increase in oxidative stress, reduced production of endothelium-dependent vasodilator, such as nitric oxide (35–37).

Arterial wall hypertrophy and endothelial dysfunction

Hypertension is closely related to vascular alterations which include decreased arterial elasticity, endothelial dysfunction, media-to-lumen ratio of small resistance arteries and capillary rarefaction (38–40). Remodelling of resistant vessels plays important role in pathophysiology of hypertension (41).

Various studies have shown that patients with acromegaly develop vascular dysfunctions such as increased arterial stiffness identified by arterial pulse wave velocity (aPWV) and reduction in blood flow-mediated dilatation which indicates an increased peripheral resistance and an impaired endothelial function (10, 42, 43).

Paisley *et al.* identified an increased aPWV in patients with acromegaly compared with that in control subjects, but no difference in aPWV between patients with active or controlled disease. Further analysis revealed correlation between arterial pulse wave velocity and age, systolic BP, acromegaly and BMI. What is important, artery stiffness is greater in acromegaly than can be accounted for by the higher systolic BP or by age (44).

Rizzoni *et al.* performed micrographic analysis of small arteries collected from subcutaneous fat of a comprising 12 normotensive, 12 hypertensive and 9 subjects with acromegaly. The study revealed structural abnormalities in acromegalics such as increased media-to-lumen ratio, media thickness and wall thickness, and that these changes can be characterised by an inward hypertrophic remodelling, rather than an eutrophic remodelling, which is more common in patients with hypertension. They also found weak correlation between media-to-lumen ratio and level of circulating IGF-I (42).

Effect of treatment on hypertension

Analysis of 5 years of long-acting somatostatin analogs therapy performed by Colao *et al.* has shown significant improvement in prevalence of hypertension from around 46.7 to 22.2% (45). In retrospective cohort study by Sardella *et al.* 58 patients were treated for 24 months with either lanreotide autogel, octreotide LAR or pegvisomant in addition to SA or as standalone therapy. The previously hypertensive acromegalics obtained significant improvement in blood pressure control in both controlled and uncontrolled disease subgroups. While hypertension developed in up to 46% of normotensive acromegalics who were unable to achieve IGF-I normalization (46).

Successful transsphenoidal surgery caused significant decrease of 24-h systolic BP (47). On the other hand, Annamalai *et al.* revealed that during 24 weeks long presurgical treatment with lanreotide autogel therapy, although there was no change in systolic and diastolic blood pressure, both aortic pulse wave velocity and flow-mediated dilatation improved (43).

Considering mentioned data successful treatment may have beneficial effect on hypertension in acromegaly, but substantial number of patients remain hypertensive despite well-controlled disease and need additional management. The guidelines recommend standard treatment with antihypertensive drugs (4,48). Due to an increased sodium reabsorption

in kidneys through the epithelial sodium channel, usage of amiloride may be a viable therapeutic option (16). Treatment of sleep apnea syndrome should be started as early as possible due to significant risk of exacerbating hypertension (4, 49).

ATHEROSCLEROSIS AND CORONARY ARTERY DISEASE

The relationship between acromegaly and coronary artery disease (CAD) according to currently obtainable data is controversial. Studies on this topic has provided conflicting results. Two studies, by Colao *et al.* (50) and Brevetti *et al.* (51), provided evidence of increased intima media in active acromegaly. However there was no increased prevalence of well-defined carotid plaques in the first and a limitation of not well matched control group in terms of equal distribution of cardiovascular risk factors in the latter (52). Other studies (53,54) negate these findings, one of them suggesting even lower IMT than in matched for cardiovascular risk factors, non-acromegalic group (53). Concluding, it seems the effect of acromegaly on IMT is secondary to cardiovascular risk factors, if any.

Aortic stiffness has been reported significantly higher, whereas aortic strain and distensibility significantly decreased in patients with active disease as compared to controls (55). These properties are positively and independently associated with atherosclerosis and predict occult CAD in general population (56).

Multiple studies suggest increased fibrinogen and MPV suggesting hypercoagulable state which is favourable to cardiovascular events (57–61).

Cannavo *et al.* assessed risk of atherosclerosis on the grounds of Agatston Score (AS) based on coronary calcifications found by multidetector computed tomography, which is considered hallmark of atherosclerosis, and Framingham Score (FS) calculation in 39 acromegalics. Authors concluded that 41% of studied subjects were at risk of atherosclerosis having increased AS or at least intermediate FS risk. Worth noting is that extent of coronary calcifications was correlated with FG and increased in patients with hypertension and diabetes mellitus but both studied parameters were not influenced significantly by control of acromegaly (62).

Conversely, Akutsu *et al.* (63) concluded that risk of CAD in acromegaly at the time of diagnosis is low and remains stable upon successful treatment.

Moreover, results from this study suggest that acromegalic patients at the time of diagnosis are even less affected by CAD than expected from the CAD risk profile in the general population. In accordance with this observation in one autopsy study, it was noted that only 11% of cases had CAD, which was less than expected from the patients' age (64). This data, until now scarce, would suggest not only lack of pro- but even antiatherogenic effect of GH/IGF-1 excess and that the prevalence of coronary artery disease is connected with regular risk factors rather than with acromegaly *per se*.

On top of that the analysis of records collected from 57 endocrine centers by Schöfl *et al.*, shows that prevalence of the myocardial infarction and stroke in patients with acromegaly treated in specialised centres was not increased compared to general population. Incidence of hypertension was higher in patients with cardiovascular event than those without, but the percentage of uncontrolled disease did not differ statistically between groups, further suggesting impact of classical risk factors but not GH/IGF-1 oversecretion (65).

Because there is no coherent evidence that acromegaly *per se* yields an additional risk on top of that resulting from known CAD risk factors, the conventional risk evaluation and prevention strategies have been proposed regarding the same guidelines as in general population (63).

ACROMEGALIC CARDIOMYOPATHY

Cardiomyopathy has been known to be connected with acromegaly since 1895 shortly after its first description (64). Its main and distinctive characteristics is cardiac hypertrophy, other are fibrosis, diastolic dysfunction impaired systolic function on exertion with decreased exercise tolerance and very rarely resting systolic dysfunction. The latter is restricted to the late stage of long-lasting active acromegaly.

Cardiac hypertrophy and its determinants

Overgrowth of the myocardium is biventricular and concentric (25). Its prevalence increases with age but occurs commonly even in young patients with relatively short, uncomplicated disease (66). Minniti *et al.* in a study of 20 acromegalic patients aged under 30 years, with normal blood pressure and glucose tolerance found evidence of cardiac hypertrophy in 20% of subjects (67). In long lasting acromegaly

prevalence of cardiomegaly may reach even 70% normotensive and 90% hypertensive patients (64).

Occurrence of cardiac hypertrophy in patients without hypertension and metabolic disorders suggests specific cardiomyopathy caused by direct effect of GH excess on heart. Both mentioned factors, however, worsen the evolution of structural or functional changes. What is more, cardiac alterations seem to be more correlated with hypertension and glucose tolerance abnormalities than GH/IGF-1 oversecretion (68). As showed by Colao *et al.* in the study of 130 subjects with acromegaly, hypertension in these patients is strongly related to prevalence and severity of cardiac hypertrophy, diastolic function and ejection fraction impairment. Diabetes and impaired glucose tolerance, on the other hand, are connected with higher prevalence of cardiac performance disturbances but not hypertrophy (68). This highlights the major role of comorbidities management in acromegaly. Indeed, in more recent studies the prevalence of cardiomyopathy is lower than earlier reported, consistent with improving quality of concomitant conditions treatment (69). Other predictors of increased left ventricle (LV) mass and detrimental functional changes are GH and IGF-I levels, age (68) and disease duration (64).

Cardiomyopathy evolution

In the early stage neither cardiac performance is affected nor does dilation of the ventricles occur. In fact, initially cardiac output increases which, together with increased heart rate and lower peripheral vascular resistance, contributes to hyperkinetic syndrome (66). Within a few years of active disease duration, subclinical diastolic dysfunction occurs due to impaired relaxation. This can lead to compromised systolic function during physical exercise when ventricular filling is essential in sustaining increased heart performance as a pump, which in turn can be manifested as decreased physical effort tolerance. In the study by Fazio *et al.* using radionuclide angiography, authors found diastolic filling times at rest reduced by 19% in acromegalic patients and 73% of them were not able to increase ejection fraction by 5% on exertion fitting criteria of impaired cardiac performance. Interestingly, diastolic dysfunction occurs in acromegaly even when other complications like hypertension, coronary artery disease or glucose metabolism abnormalities are absent (70).

Finally, full-blown cardiomyopathy develops manifesting as dilation of the ventricles and resting systolic dysfunction with clinical signs of heart

failure with reduced ejection fraction. However, it occurs rarely in approximately 3% of patients and is largely limited to subjects with long-lasting untreated acromegaly (71). Once developed, it severely worsens prognosis: Bihan *et al.* reported that 1- and 5-year mortality rates for patients with heart failure were 25 and 37.5%, respectively (71).

Pathophysiology

It is not easy to explain the deleterious structural changes in heart occurring in long-lasting acromegaly as a direct consequence of GH/IGF-I *per se* (72). Short term GH or IGF-I excess seems to have rather beneficial than detrimental effects on heart. Via receptors for both molecules in heart it stimulates synthesis of contractile proteins, balanced growth of cardiomyocytes and interstitial elements (resulting in lack of fibrosis) and provides a model of physiological cardiac growth with unaltered capillary density and beneficial effect on myocyte short/long axis ratio (72). It also exerts positive influence on calcium ions influx and peak calcium ion levels in cardiomyocytes resulting in increased contractility and functional advantage (73). In some studies GH administered exogenously exerted favourable effects in patients with dilated cardiomyopathy. It was also shown in animal studies to prevent post infarction ventricular necrosis, apoptosis and remodelling. Complementing observations are that GH deficiency is linked with worse systolic function which improves after institution of replacement therapy and that subjects with lower IGF-I levels in the immediate postinfarction period had better cardiac performance and overall outcomes (72).

Yet it seems, that at some currently undetermined point of time changes in heart induced by GH excess become maladaptive and eventually lead to cardiac failure in acromegaly.

As showed by the autopsic study of 27 acromegalic patients conducted by Lie *et al.* histological findings in acromegalic heart are signs of myocarditis with lymphomononuclear cell infiltrates, necrosis, extensive replacement fibrosis and derangement of organ architecture (64). Frustaci *et al.* (74) reported 8-fold increase in fibrosis in endomyocardial biopsies from acromegalic patients in advanced stage of the disease comparing to controls, which consisted of matched for age and sex patients after mitral valve replacement. What is more, authors found 495-fold and 305-fold increase in apoptosis of myocytes and nonmyocyte elements, respectively. This form of cell

death can significantly impact myocardial mechanics by reducing the force-generating capacity of the muscle as well as the ability of developing resting tension with changes in sarcomere length. It also plays crucial role in development of non-acromegalic cardiomyopathy (75,76). Indeed in the mentioned study the magnitude of myocyte apoptosis correlated with the extent of ejection fraction impairment. Degree of apoptosis as well as fibrosis was positively correlated with the duration of the disease.

On the contrary, in two more recent studies using MRI found low prevalence of fibrosis in studied population. In one study authors reported fibrosis in 3.5% (69) and in the another 14% of studied subjects in comparison to up to 85% in earlier autoptic studies (64). Authors pointed out that fibrosis may not have a relevant role in cardiac function in acromegaly, at least in these studied populations. The discordances may result from the worse control of comorbidities in the studied populations in the past that could have an important role in development of fibrosis (54).

Effect of treatment

Effective treatment can not only arrest the unfavourable structural and functional changes but also reverse them. Surgical cure as well as the use of medication (SA, pegvisomant) are both successful in this concern.

In a meta-analysis of 18 studies involving 290 patients treatment with SA has been shown to reverse cardiac hypertrophy, improve diastolic function, exercise tolerance and normalise impaired cardiac performance on exertion. A trend towards increase in systolic function has been observed (77). Excellent clinical response to octreotide in patient with acromegaly and dilated cardiomyopathy with reduced ejection fraction and recurrent pulmonary oedema who was a possible candidate for heart transplant has been reported (78).

The outcomes of pegvisomant and successful surgery are similar. Reduction in left ventricular hypertrophy indices and improvement in diastolic and systolic function parameters have been demonstrated for both treatment modalities (47, 79).

Fact that the treatment targeting GH levels reverses cardiac abnormalities further supports existence of specific acromegalic cardiomyopathy.

Interestingly, receptors for somatostatin, including ss2 and ss5 - which are target receptors for octreotide and lanreotide, are expressed on cardiac myocyte and interstitial cells (80). This

raises a question about involvement of direct effect on heart of these drugs on their positive outcomes in acromegaly. In support of this theory De Mainis *et al.* show significant reduction of left ventricular mass in patients receiving SA treatment regardless of biochemical control.

Considering cardiomyopathy, the GH-lowering treatment is most beneficial when implemented early in the disease course, in young patients. For example Colao *et al.* observed normalisation of left ventricular hypertrophy and rise in LVEF on peak exercise in 100% and 80%, respectively in patients aged < 40 years and in less than 50% in patients aged > 40 years (81).

ARRHYTHMIAS

Cardiac rhythm have been less studied in acromegaly patients than the structural heart changes. LV hypertrophy and fibrosis, both reported as common findings in acromegaly, are associated with a higher incidence of arrhythmias and sudden death in many conditions other than acromegaly like hypertension or ischaemic heart disease. Fibrosis and connected with LV hypertrophy myofibrillar dearangement with anatomical uncoupling of cardiomyocytes may lead to slowed and non-homogenous conduction of action potential further leading to arrhythmias. Meta-analysis of studies including over 27,000 subjects (not suffering from acromegaly) found the odds ratio for supraventricular and ventricular arrhythmias to be 3.4 and 2.8 respectively in patients with left ventricular hypertrophy (82). Numerous studies show correlation between the amount of collagen in cardiac tissue and incidence of arrhythmias (83).

In studies by Herrmann *et al.* and Maffei *et al.* high prevalence of late potentials were observed. Late potentials (LPs) consist of low amplitude and high frequency signals in the terminal part of the QRS complex recorded in a signal-averaged electrocardiogram. Their occurrence is considered a predictor of serious ventricular tachyarrhythmias and can be associated with an increased risk of sudden cardiac death during the subsequent year (84). Both studies reported incidence of LPs in 23% patients with acromegaly which was significantly higher than in healthy control groups. In study by Herrmann *et al.* the prevalence was particularly high in patients with active acromegaly and reached 56% compared to 6% in cured/well-controlled group. The association with the active disease was independent of age, gender, duration of the disease and body mass index. On the contrary, Maffei found significant correlation with the duration but not activity of the disease. The

correlation with disease duration would be expected considering that fibrosis is more frequent in long-lasting disease. Importantly authors observed correspondence of LP-positivity with premature ventricular complexes detected in 24-hour Holter monitoring for the first time demonstrating arrhythmogenic potential of LPs in acromegaly however more studies are required to drive a substantial conclusions in this matter.

In a study by Kahaly *et al.* (85) authors found complex ventricular but not supraventricular arrhythmias to be significantly more prevalent and severe in patients than in controls in 24-h ECG Holter monitoring. Abnormalities were detectable in 48% of patients compared to 12% in controls. Frequency correlated with disease duration while severity with cardiac hypertrophy.

Rodrigues *et al.* (86) reported ventricular arrhythmias in 41% studied patients with acromegaly, however among the 14 reported 12 were asymptomatic ventricular extrasystoles which are commonly found in healthy subjects and most often considered not clinically important, the other two were asymptomatic ventricular bigeminism and ventricular tachycardia in a patient with ischaemic heart disease.

Conversely, Warszawski *et al.* found no clinically relevant arrhythmias in 24-h ECG Holter monitoring neither in treatment naive acromegalics nor in patients after 1 year of SA treatment. Possible explanation of this finding could be the fact that in the study population only two patients presented left ventricular hypertrophy and only three had fibrosis detected by MRI, indicating at the same time that rhythm disturbances in acromegaly are limited to patients with structural abnormalities.

Particular rhythm abnormality known LV dyssynchrony can be associated with acromegaly. It is defined as the loss of the simultaneous peak contraction of corresponding cardiac segments. Kırış *et al.* in the study performed on group of 60 patients, 30 of whom had active acromegaly reported higher prevalence of LV hypertrophy in acromegalics compared to control group and it significant correlation with LV dyssynchrony. Authors also reported notable correlation between GH and IGF-I levels and interstitial fibrosis (87).

Concluding, there is some data providing evidence that patients with acromegaly are at high risk of arrhythmias, especially those with structural cardiac abnormalities, however, for this relationship to be well-established it still needs to be studied more extensively.

HEART VALVE DISEASE

Pathophysiological background of valve disease in acromegaly is based on the unmediated effect of GH and IGF-I on connective tissue manifesting as dysregulation in metalloproteinases expression, proteoglycan synthesis as well as collagen and mucopolysaccharides deposition.

Valve abnormalities may be further aggravated by acromegaly aortic root dilatation which had been connected with acromegaly and documented in about 26% of a 42 patients in one study (88). This condition was in turn positively correlated with left ventricular mass.

The findings of heart valve disease in acromegaly consist of aortic and mitral regurgitation. Lie *et al.* (64) found mitral and aortic abnormalities in 19% of their autopsy series.

Pereira *et al.* (89) in the echocardiographic study of 40 patients with acromegaly found aortic regurgitation in 30% and mitral regurgitation in 5% of patients. These values were statistically significantly higher than in matched controls in which they totalled 7 and 0%, respectively. Furthermore, authors pointed out that frequency of valvular abnormalities correlates with duration of disease and calculated that there was 19% increase in odds ratio with every year of GH excess duration.

Even higher prevalence was reported by Colao *et al.* (90) who found 86% of 42 studied active and 74% cured patients with acromegaly affected by valve disease predominantly aortic regurgitation. Both values significantly differed from controls matched for each group in which prevalence was 24% and 9% respectively. Cardiac valve abnormalities were more frequent in individuals with left ventricular hypertrophy in both groups, however in acromegaly, but not in controls, valve dysfunction was also highly prevalent in subjects with normal ventricular mass occurring in 75% active and 54% cured patients.

Van der Klaauw *et al.* (91) in observational study performed on 37 acromegalics investigated change in the prevalence of valve regurgitation with time in active and controlled disease in the mean follow up of about 2 years. Authors found a significant increase from baseline 56% to 88% in active and no change in controlled disease, further documenting cumulative effect of GH overexpression on deterioration of valve function. The results also pointed out the irreversible but stable character of this abnormality in inactive acromegaly. Additionally investigators found, conversely to study by Colao *et al.*, no association of valve dysfunction with left ventricular hypertrophy, thus demonstrating

that the effect of GH excess on connective tissue rather than changes in ventricular diameter is the cause of this complication in studied population.

In con, acromegaly is associated with high incidence of heart valve disease, predominantly aortic regurgitation, which increases with the disease duration. Successful treatment of acromegaly, understood as achieving hormonal normalisation, does not undo the valve damage, but reduces its further worsening.

Although recent data (92) suggest decreased role of traditional cardiovascular complications reflecting mortality of acromegalic patients, it still remains an important factor. Relative normalization of mortality rates together with biochemical control of the disease in the last decade is caused by greater efficacy of neurosurgery and adjuvant medical therapies. In addition increased life expectancy recently shift from circulatory to cancer related deaths during long term follow up has been observed (93). Nevertheless, cardiovascular mortality risk must be taken in consideration in the patients with acromegaly, especially those with uncontrolled disease due to delayed diagnosis or lesser availability of modern efficacious therapies.

Conflict of interest

The authors declare that they have no conflict of interest.

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