IMPACT OF ACROMEGALY ON THE CARDIOVASCULAR SYSTEM

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IMPACT OF ACROMEGALY ON THE CARDIOVASCULAR SYSTEM (Abstract): Cardiovascular manifestations occur in 60% of patients with acromegaly. The severity of the structural and functional heart abnormalities mainly depends on the levels of growth hormone and insulin-like growth factor 1 and the time between disease onset and diagnosis. Long-lasting elevated hormone levels are responsible for acromegalic cardiomyopathy, valvular disease, arrhythmias, hypertension, coronary artery disease and even congestive heart failure. We highlight the tremendous impact of hormone imbalance upon the heart structure and function in order to raise awareness upon the fact that cardiovascular disease has become the leading cause of mortality in patients with acromegaly. We draw attention to the fact that acromegaly is more than an endocrine disease and we emphasize the need for a multidisciplinary approach of the acromegalic patient, of which the cardiologist must be part.
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Acromegaly is a rare endocrine disorder caused by prolonged and excessive secretion of growth hormone (GH) by the pituitary gland. GH exerts its effects either directly or indirectly, through its peripheral effector insulin-like growth factor 1 (IGF-1). Long-lasting high levels of these hormones lead to enlargement of organs and soft tissues.

Cardiovascular manifestations occur in 60% of patients. The cardiovascular impact of hormonal imbalance manifests as cardiomyopathy, valvular disease, arrhythmias, hypertension, coronary artery disease and even congestive heart failure if acromegaly is uncontrolled. Cardiovascular disease has become the leading cause of mortality in patients with acromegaly (1), especially in the presence of diabetes mellitus and obstructive sleep apnea, which are highly prevalent in these patients.

Acromegalic cardiomyopathy

Cardiac involvement in the absence of other identifiable causes of cardiomyopathy defines acromegalic cardiomyopathy. It

affects 3% of patients with acromegaly. The severity of the structural and functional heart abnormalities mainly depends on the levels of GH and IGF-1, and the period of time when the heart was exposed to elevated hormone levels (the time between disease onset and diagnosis) (2).

Acromegalic cardiomyopathy evolves in three stages (3). The characteristics of the first stage are enhanced myocardial contractility, increased cardiac output and decreased peripheral vascular resistance. It is the so called "hyperkinetic syndrome" (4). IGF-1 increases Ca^{2+} influx and raise peak Ca^{2+} levels in cardiomyocytes and also increases the sensitivity of myofilaments to Ca^{2+}, thus resulting in increased inotropism and a hyperkinetic heart (5).

The intermediate stage is characterized by biventricular hypertrophy, interstitial fibrosis, diastolic dysfunction and impaired systolic function during exercise (4, 6). The ventricular walls are concentrically thickened due to a relative increase in myocyte size. Usually, hypertrophy of the left ventricle is more significant, but the right ventricle can be equally involved. Hypertrophy without ventricular dilation is an early feature of the disease. Studies show that up to 54.5% of young patients (<40 years old) with active acromegaly of 3-7-year duration had echocardiographic evidence of left ventricular hypertrophy. This percentage rises up to 72.2% in patients aged 41-60 years and disease duration of 5-15 years (7). Interstitial fibrosis, consequence of a markedly increased myocyte apoptosis (495 fold higher than normal) is associated with extracellular collagen deposition and myofibrillar derangement (8). The damaged heart architecture has a negative impact on ventricular function. Ventricular relaxation is impaired, and compliance is reduced. These changes lead to diastolic dysfunction. Left ventricular filling is insignificantly impaired at rest but is associated with reduced exercise tolerance.

In the final stage, severe enlargement of cardiac chambers and systolic and diastolic dysfunction occur (4). The peripheral vascular resistance increases. This late stage ends in congestive heart failure.

Successful treatment of acromegaly is associated with a decrease in left ventricular mass and with the improvement of diastolic and systolic function (9). A beneficial effect of treatment has also been reported in patients with acromegalic cardiomyopathy and congestive heart failure (10). Cardiac function improvement is greatest in young patients with short disease duration, in which the early diastolic changes are completely reversible under treatment.

Arrhythmias in acromegaly

Patients with acromegaly have a high incidence of arrhythmias (11). Cardiac arrhythmias and sudden cardiac death are the most common causes of increased mortality in acromegaly. Abnormal heart architecture, with areas of hypertrophied myocytes separated by fibrosis and cellular infiltration provide de substrate for the structural uncoupling of cardiac myocytes. Other mechanisms like phenotypic changes in membrane proteins and conduction system disease are also involved (12), but fibrosis is mainly responsible for the disorganized and asynchronous electrical activity in ventricles, favoring reentrant events.

The electrophysiological abnormalities have a wide range of manifestations, from ectopic beats, paroxysmal atrial fibrillation,

paroxysmal supraventricular tachycardia, sick sinus syndrome, to ventricular tachycardia and bundle branch blocks (6,13). One study reported conduction disorders in up to 41% of patients with acromegaly (14).

Arrhythmic events are present at rest, but especially during exercise. The frequency and severity of ventricular arrhythmias correlate with clinical activity score, duration of acromegaly and left ventricular mass, but not with hormone levels (12). This is supported by several studies (14,15) that showed that ventricular arrhythmias were as frequent before as after treatment of acromegaly, implying that fibrous tissue infiltration had resulted in permanent irreversible scarring.

Hypertension in acromegaly

Hypertension is the cardiovascular disease most frequently encountered in acromegaly patients, with a reported prevalence ranging from 25 to 50% (5). The diastolic blood pressure is usually elevated (16). The pathogenesis of HTA in acromegaly is multifactorial, including increased vascular resistance, increased plasma volume, alterations in renin-angiotensin-aldosterone system and insulin resistance (9). Long-lasting high GH levels stimulate smooth muscle cell growth, thereby increasing peripheral vascular resistance and blood pressure (5). Moreover, GH blocks insulin actions at several levels, leading to insulin resistance (17), which is associated with low nitric oxide production and high activity of the vascular renin-angiotensin-aldosterone system (9). The impaired endothelium-dependent vasodilation, the increased vascular response to angiotensin II and the exaggerated sympathetic-mediated vasoconstrictor response contribute in various degrees to the increase of arterial peripheral resistance (18, 19).

GH can cause sodium retention through three mechanisms: activation of Na^+-K^+ ATP-ase pump in the renal tubules (20), activation of the renin angiotensin system and inhibition of atrial natriuretic peptide release (21). Due to its antinatriuretic action, GH increases extracellular volume and by consequence blood pressure.

It is important to highlight the fact that hypertension is an independent risk factor for cardiac morbidity in acromegalic patients and an important negative prognostic factor for mortality in these patients.

Valvular disease in acromegaly

Few data are available regarding valvular disease in acromegaly because it rarely occurs (11). Mitral, aortic and tricuspid regurgitation have been reported in the late stages of disease, usually as a result of ventricular remodeling. One small study (22) including 32 patients with acromegaly found aortic regurgitation in 31%, mitral regurgitation in 47%, and tricuspid regurgitation in 37% of the cases. Another study (23) described mitral and aortic valvular annulus fragility and leaflet disarray, accompanied by functional regurgitation.

Coronary artery disease in acromegaly

Data regarding coronary artery disease (CAD) in acromegaly are limited and conflicting (11,24). There is much evidence that acromegaly per se does not increase the risk of CAD (25). Calculations based on the European Society of Cardiology risk score and Framingham risk score showed a

low 10-year CAD risk (9). These findings were supported by studies using coronary artery calcium (CAC) score with the purpose of identifying early-stage coronary atherosclerotic disease in asymptomatic patients, in which low scores have been obtained.

Conversely, a study (26) that evaluated the risk factors and CAC score showed that 41% of acromegalic patients are at risk for coronary atherosclerosis and that coronary calcifications were evident in about half of cases. These findings are consistent with the fact that acromegaly is an insulin-resistant state, associated with a high prevalence of diabetes mellitus and hyperlipidemia, which contribute to the cardiovascular risk.

CONCLUSIONS

Our research shows that acromegaly is far more than an endocrine disease. We highlight the major influence of GH and IGF-1 on cardiovascular system. Morphological and functional heart abnormalities induced by long-lasting high hormone levels have a tremendous impact upon mortality, morbidity and quality of life in acromegalic patients. We encourage the close collaboration between endocrinologists and cardiologists in order to ensure an early diagnosis and adequate monitoring of cardiovascular consequences of acromegaly. Since many parameters of cardiac function change with acromegaly treatment, we emphasize the need of periodical cardiovascular assessment.

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