Insulin and insulin-like growth factor-I: two of a kind in the development of cardiovascular disease?
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Chapter 8

Case report: Low circulating IGF-I levels due to Acid-Labile Subunit deficiency in adulthood are not associated with early development of atherosclerosis and impaired heart function.

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ABSTRACT

Objective
Decreased insulin-like growth factor-I (IGF-I) levels in adults have been associated with an increased risk of ischemic heart disease and heart failure. It is currently unknown whether patients with low circulating IGF-I levels due to a homozygous acid-labile subunit (IGFALS) gene mutation also have increased risk of cardiovascular disease. Therefore, we evaluated atherosclerotic burden in a 27 year old male patient who was diagnosed with a homozygous IGFALS mutation and consequently had extremely low circulating IGF-I levels.

Methods
Ten year’s cardiovascular risk was calculated using the Framingham risk score. Presence of (subclinical) atherosclerosis was assessed using a 64-slice CT scan of the coronary arteries. Cardiac performance was measured by conventional echocardiographic measurements, three dimensional (3D)-echocardiography, and tissue deformation imaging.

Results
Despite his extremely low circulating IGF-I levels due to Acid-Labile Subunit (ALS) deficiency, our patient had a low Framingham risk score and no signs of coronary atherosclerosis. Adjusted for physical height, cardiac performance was not impaired compared with healthy subjects.

Conclusion
The present case report does not lend support to routine cardiovascular screening in patients with extremely low circulating IGF-I levels due to a homozygous IGFALS mutation, when cardiovascular risk is low.
INTRODUCTION

The protein Acid-Labile Subunit (ALS) plays an important role in prolonging the half-life of insulin-like growth factor-I (IGF-I) and its principal binding protein IGF binding protein-3 (IGFBP-3) in the circulation. At present, 21 patients with homozygous or compound heterozygous mutations in the IGFALS gene have been reported. These IGFALS gene mutations all result in undetectable or extremely low circulating ALS levels and, consequently, extremely low circulating levels of IGF-I. During childhood, these patients are characterized by growth retardation and a mild insulin resistance. In adulthood, however, less is known about the clinical presentation of ALS deficiency.

Low IGF-I levels in healthy middle-aged populations have been associated with increased risk of ischemic heart disease and increased risk of developing congestive heart failure. Additionally, once heart failure is clinically present, it has been shown that low IGF-I levels are associated with a worse prognosis. Furthermore, patients with adult onset growth hormone deficiency (AGHD) and subsequent low IGF-I levels generally have a reduced peak exercise cardiac performance and an increased atherosclerotic burden that is reflected by an increased intima media thickness of the carotid arteries. These findings suggest that low IGF-I status in adulthood may have implications for the development or progression of cardiovascular disease (CVD).

In this context, an extremely low IGF-I status from childhood onwards (as seen in ALS deficient patients) might be expected to contribute to the early development of atherosclerosis and impaired cardiac function, warranting routine cardiovascular screening in adults that carry an IGFALS mutation. Therefore, we evaluated the cardiovascular risk profile, including cardiac performance and atherosclerotic disease burden, in a 27 year old patient carrying a homozygous IGFALS gene mutation. Furthermore, we reviewed the currently existing literature concerning low IGF-I in adulthood and its possible involvement in the development of CVD.

METHODS

Evaluation of cardiovascular risk profile

In order to assess the global cardiovascular risk profile, a cardiovascular medical history was taken and a physical examination was performed. Additionally, total body fat percentage was measured with a DEXA scan. An electrocardiogram (EKG) at rest was made to detect the possible presence of axis deviation, rhythm disturbances or ischemia-related changes in conformation. Fasting venous blood was drawn to determine the lipid and glucose profile. The patient gave written informed consent for publication of current data.
Evaluation of atherosclerosis in coronary arteries

In order to evaluate the presence of subclinical premature atherosclerosis in the coronary arteries, we performed 64-slice CT scanning of the heart (Brilliance 64, Philips Medical Systems, Cleveland, OH). Scan protocol and image reconstruction have been described in detail previously.\textsuperscript{10,11}

Cardiac performance

Cardiac performance was assessed by conventional echocardiographic evaluation, three dimensional (3D)-echocardiography, and tissue deformation imaging (both Doppler and speckle-tracking derived). Echocardiographic examination was performed with the patient at rest, lying in a left lateral decubitus position. Ultrasound data were acquired using a Vivid 7 scanner (GE Vingmed ultrasound, General Electric, Milwaukee, Wis) with a broadband M3S ultrasound probe and a matrix-array probe for the 3D image acquisition. A complete echocardiographic analysis was performed in two-dimensional (B-mode) and tissue Doppler imaging (TDI) modes. For 3D-echocardiographic examination we used a matrix transducer for transthoracic apical acquisitions during a 5–7 s breath-hold. Care was taken to include the entire LV volume within the pyramid-shaped 3D scan-volume. Commercially available software (4D LV-Analysis, TomTec Imaging Systems, Munich, Germany) was used for quantification of global LV function. Diastolic function was assessed by pulsed wave Doppler (inflow velocities and mitral annular velocities). Both standard parasternal views (long and short axis) and apical views (4-, 2- and 3-chamber) were obtained. In order to detect differences in ventricular wall motion, we performed tissue deformation imaging. For more detailed information we refer to prior published work.\textsuperscript{12}

RESULTS

General patient characteristics

For an extensive description of the patient with regard to the \textit{IGFALS} mutation and its associated phenotype, we refer to our prior published report.\textsuperscript{9} In short, the patient was born at term (weight and length unreported) as the eldest of four children of consanguineous Kurdish parents. He had a significant delay in puberty onset and his growth curve, from the age of 14 years onwards, ran parallel to (but far below) the -2 SDS growth line of the Turkish reference diagram. He reached a final height of 149.7 cm (-4.2 SDS). At the age of 16 years, he was referred to a university hospital for analysis of his growth impairment. During cardiologic investigation a grade I mitral valve and a mild tricuspid valve insufficiency were detected. At the age of 20 years, extensive biochemical evaluations revealed an elevated growth hormone (GH) peak of 63 mU/L after exercise (equivalent to 21 mg/L, conversion rate 1 μg/L = 3.0 IU, standard WHO IS 110 98/574), and significantly decreased levels of both IGF-I (16-38 ng/mL, -6.9 to -5.0 SDS) and IGFBP-3 (0.2 mg/L, -12.0 SDS). There was a poor response to GH with
two different doses (0.8 and 1.6 mg/m²) in an IGF-I generation test: on the low GH dose IGF-I did not rise (38 and 35 ng/ml) but on the higher GH dose IGF-I increased from 16 to 60 ng/ml. IGFBP-3 did not change in this test. ALS was not detectable in plasma.

**Evaluation of cardiovascular risk profile**

At the time of cardiovascular risk assessment our patient was 27 years of age. He had no positive family history with regard to premature cardiovascular disease, atherothrombosis or type 2 diabetes. He did not use any medication or over the counter medication, nor did he smoke. His height was 149.7 cm and body weight was 50 kg, resulting in a BMI of 22.3 kg/m². Body surface area (BSA), calculated with the DuBois and DuBois formula\(^\text{13}\), was 1.43 m². A continuous automatic blood pressure registration for 30 minutes revealed an average blood pressure of 120/75 mm Hg with a regular pulse rate (measured in rest and in supine position) of 60 bpm. Total body fat percentage was estimated at 25%. The EKG did not show any abnormalities such as rhythm disturbances or ischemia related changes in conformation. Results of fasting venous blood sampling analysis are presented in table 1. Our patient showed borderline mild insulin resistance and total cholesterol and triglyceride levels were elevated. No micro-albuminuria was present. A Framingham risk score revealed an individual risk of 1% for a cardiovascular event in ten years.

**Table 1. Glucose and lipid profile.**

<table>
<thead>
<tr>
<th></th>
<th>Reference values</th>
</tr>
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<tbody>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>7.2</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>n.a.</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.2</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>4.8</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.6</td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>5.6</td>
</tr>
<tr>
<td>HbA1C (mmol/mol)</td>
<td>38</td>
</tr>
<tr>
<td>Insulin (mU/L)</td>
<td>11</td>
</tr>
</tbody>
</table>

n.a. not applicable

**Evaluation of atherosclerosis in coronary arteries**

Multi-slice CT-scanning of the heart did not reveal any atherosclerotic lesion in all evaluated coronary segments. No atherosclerotic plaques, coronary calcifications or other abnormalities were found in the right and left coronary artery system (fig 1). No increased deposition of calcium was found on the aortic valves and no other cardiac abnormalities were detected.
Case report: ALS deficiency and cardiovascular disease.

Figure 1. Evaluation of coronary system and cardiac anatomy by multi-slice CT scanning.
a, b: Volume rendered CT image of the coronary arteries. c, d, e: curved multiplaner reconstructed images of the coronary arteries showing no coronary artery disease. RCA: right coronary artery; LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery

Figure 2. Speckle tracking derived regional and global deformation.
The regional deformation graphs are shown in the individual 16 LV-segments in the three different imaging planes (LAX, A2C en A4C). The graphs show normal systolic deformation values as well as normal graph characteristics (i.e. no post-systolic shortening or dyskinesia), both indicative of normal regional systolic function.
Abbreviations: LAX: apical long axis; A2C: apical 2-chamber; A4C: apical 4-chamber; AVC: aorta valve closure
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Table 2. Cardiac performance assessed by 3D-echocardiographic analysis

<table>
<thead>
<tr>
<th></th>
<th>Absolute value</th>
<th>BSA corrected</th>
<th>Reference value²⁸</th>
</tr>
</thead>
<tbody>
<tr>
<td>End diastolic volume</td>
<td>84.6 ml</td>
<td>59.2 (ml/m²)</td>
<td>58.7 ± 11.0 (ml/m²)</td>
</tr>
<tr>
<td>End systolic volume</td>
<td>35.4 ml</td>
<td>24.8 (ml/m²)</td>
<td>23.6 ± 5.8 (ml/m²)</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>49.2 ml</td>
<td>-</td>
<td>48.3 ± 8.4 ml</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>58.2%</td>
<td>-</td>
<td>60.1 ± 3.2 %</td>
</tr>
</tbody>
</table>

**Cardiac performance**

All conventional measures of anatomy and systolic and diastolic function, measured by echocardiography, did not show any abnormalities (compared with reference values adjusted for sex, age and BSA). There were no signs of valvular insufficiency. The 3-D findings are summarized in table 2. Adjusted for patient’s decreased BSA, all variables were within reference ranges. The quantitative analysis for abnormalities in regional deformation showed a normal wall strain pattern and peak systolic value for all left ventricular wall segments (figure 2) and right ventricle. The Doppler derived deformation was in concordance with the speckle tracking findings.

**DISCUSSION**

Adult subjects with low circulating IGF-I levels have been considered to be at increased risk of developing premature atherosclerosis and/or heart failure. Despite extremely low circulating IGF-I levels, due to an ALS deficiency, our 27 year old patient had no increased cardiovascular risk profile, as reflected by the absence of any sign of (subclinical) coronary atherosclerosis. The assumption that all patients with ALS deficiency and subsequent low circulating IGF-I levels should be extensively screened for cardiovascular disease after they reached adulthood should therefore be reconsidered.

Literature about ALS deficiency has mainly focussed on the consequences of low IGF-I levels on growth.¹⁴ Very little is known about the consequences on CVD. We should therefore be aware that most of today’s knowledge about low IGF-I levels and CVD concerns data extrapolated from other clinical conditions that are characterized by a low IGF-I status. In this respect it is important to realize that IGF-I levels can be low for several reasons. First of all, IGF-I levels can be low, but still within, or near to, the reference range, as a consequence of the normal spread within the general population. Secondly, congenital GH deficiency (GHD) or GH Insensitivity Syndrome (Laron syndrome) lead to extremely low circulating IGF-I levels. In the third place, extremely low IGF-I levels can also be caused by adult onset GH deficiency (AGHD) as a result of (pan)hypopituitarism after hypophysectomy or irradiation of the pituitary gland, because of a pituitary adenoma. In patients with GH deficiency or insensitivity, IGF-I
is not only low in the circulation, but also in all GH-responsive tissues. Fourthly, circulating IGF-I can be low due to ALS deficiency, where the tissue IGF-I is assumed to be normal. Hence, patients with a low IGF-I status should be considered a heterogenous population and cannot be all lumped in the same category.

The association between low IGF-I levels and CVD has mainly been studied in healthy populations and in patients with AGHD. Epidemiologic studies in healthy populations have demonstrated an association between low IGF-I levels and increased risk of ischemic heart disease or heart failure.\textsuperscript{2,5} It should be acknowledged, however, that subjects included in these studies generally were middle aged or older, which makes it complicated to extrapolate the results to young adults who have extremely low IGF-I levels from childhood onwards. Furthermore, there are also many recent prospective cohort studies which did not observe an association between IGF-I levels and (ischemic) heart disease,\textsuperscript{15-20} and one prospective study even reported a decreased risk of heart failure when IGF-I levels were low.\textsuperscript{18} Taken together, the role of IGF-I status on CVD in healthy middle aged subjects is currently unclear.

Adults with untreated GH deficiency and subsequent low IGF-I levels due to hypopituitarism, are known to have an increased risk of premature atherosclerosis and decreased heart function.\textsuperscript{8} The cause of this increased CV risk is currently unknown. AGHD is often accompanied by central adiposity, dyslipidemia and hypertension. Consequently, patients with AGHD have a more than two-fold increased prevalence of the metabolic syndrome in comparison with controls\textsuperscript{21} which could contribute to increased CV risk. Substitution of GH in these patients is known to decrease body fat mass and to reduce CV risk.\textsuperscript{8} Whether this decrease in CV risk could also be attained by substitution with IGF-I has not been studied. Furthermore, it appears that inappropriate replacement of other hormones, like sex hormones or corticoids, in hypopituitarism patients can contribute to insulin resistance and CVD. Patients that receive glucocorticoid doses of more than 20 mg per day have a worse metabolic profile, with higher BMI, total cholesterol, LDL-cholesterol, and triglycerides, compared with patients receiving less than 20 mg per day.\textsuperscript{22} Therefore, rigid hormone substitution in patients with AGHD may influence CVD development beyond low IGF-I status. This implicates that the raised CV risk that accompanies AGHD can not only be attributed to low IGF-I status. Hence, it is unwarranted to presume that patients with low IGF-I levels due to AGHD are comparable to patients with low IGF-I levels due to an IGFALS mutation with respect to cardiovascular risk profile and atherosclerosis.

Our patient has extremely low circulating IGF-I levels due to an IGFALS mutation. Although we did not find any effect of low circulating IGF-I levels on atherosclerosis, we could not assure whether his low IGF-I status might have harmful effects on heart repair after a possible future cardiovascular event. Indeed, low serum IGF-I levels have been associated with a poor prognosis after a myocardial infarction.\textsuperscript{23,24} Furthermore, with the currently available laboratory tests, it is impossible to measure local autocrine/paracrine IGF-I secretion. Theoretically, patients with a genetic ALS defect are expected to have a normal autocrine and paracrine IGF-I production, which is probably the reason that their growth is far less disturbed than in patients with a
complete GH deficiency, GH insensitivity syndrome (Laron syndrome) or IGF-I deficiency.\textsuperscript{14} Additionally, ALS deficient patients are expected to have normal or even increased GH levels, which will stimulate autocrine and paracrine IGF-I production. Local IGF-I status within the heart plays an important role in the repair mechanisms after ischemia. IGF-I overexpression within the heart of mice protects against myocyte apoptosis and ventricular dilatation after infarction.\textsuperscript{25} Moreover, local IGF-I therapy in the heart after cardiac ischemia improves myocardial function.\textsuperscript{26,27} With an aging population of patients with an \textit{IGFALS} mutation, these observations could be of interest, especially for those patients with concomitant premature cardiovascular disease in their family history. In these patients, both elevated GH levels and local unaffected IGF-I production may prevent early manifestations of symptoms of CVD. The normal cardiac performance of our patient supports the assumption that local IGF-I production is undisturbed in patients with ALS deficiency.

In summary, the consequences of low IGF-I levels due to \textit{IGFALS} mutations on cardiovascular disease development are currently unknown. Epidemiologic studies which have assessed the association between IGF-I levels and CVD are inconsistent and have been performed in populations that are not comparable to young adults with an \textit{IGFALS} mutation. Therefore, we extensively evaluated cardiovascular disease status in a 27 year old male patient with a homozygous \textit{IGFALS} mutation and subsequent low circulating IGF-I levels. Besides a mild insulin resistance and lipid disturbances we did not find any sign of (subclinical) CVD. These results suggest that low circulating IGF-I status due to an \textit{IGFALS} mutation is not necessarily accompanied by increased risk of CVD. Although we think that ALS deficient patients should not be submitted to extensive cardiovascular screening when cardiovascular risk is low, more research is needed, especially in older patients with ALS deficiency. Future long-term prospective studies, including more and older patients with \textit{IGFALS} mutations, hopefully will elucidate whether extreme low circulating IGF-I levels in these patients on a longer term will affect CVD, or whether locally produced IGF-I will protect against (progression) of CVD.
REFERENCE LIST


Case report: ALS deficiency and cardiovascular disease.

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