

Late Recognition of Andersen's Disease in Advanced Heart Failure

Zakaria Wakrim ^{a*}, Chaimaa Ait Elqadi ^a, Imane Essaket ^a, Mohamed El Jamili ^a
and Mustapha Hattaoui ^a

^a Department of Cardiology, Mohammed VI University Hospital, Marrakesh, Morocco.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Glucogen storage diseases such as Andersen's disease are inherited disorders of carbohydrate metabolism. Cardiac involvement in Andersen's disease is extremely unusual and difficult to diagnose, especially in elderly individuals with atypical presentations. The following is a case of a 61-year-old man with a family history of muscle weakness who presented with congestive heart failure and was found to have Andersen disease cardiomyopathy. The diagnosis was made in view of the normal negative workup for cardiomyopathy, massive glucose tetrasaccharide excretion, and normal alpha-glucosidase activity. The patient rapidly deteriorated and passed away. This case highlights the need to consider storage diseases in adults with nonischemic dilated cardiomyopathy of uncertain etiology in the presence of liver or muscle involvement.

Keywords: Andersen' disease; GSD; heart failure; dilated cardiomyopathy.

1. INTRODUCTION

Glycogen, stored in the muscles and liver, is the body's main source of energy. Various enzymes break down glycogen into glucose when needed.

Glucogen storage diseases (GSD) or glycogenosis diseases are rare hereditary diseases of carbohydrate metabolism. The GSD types are categorized from I to IV according to the enzyme that is deficient in each type.

*Corresponding author: E-mail: contact.wakrim@gmail.com;

Glycogen storage disease type IV (also named polyglycosan body disease, amylopectinosis or Andersen's disease) is a rare autosomal recessive disorder caused by a deficiency of glycogen branching enzyme (GBE) activity in the liver as well as in other tissues. This shortage leads to precipitation of glycogen in organs, mainly the liver and heart [1]. The extent of the disease depends on the amount of the enzyme produced.

Andersen's disease has five different variants with diverse clinical manifestations and tissue involvements [1,2]. In adults, GBE activity is higher and symptoms do not appear until later in life [3], cardiac compromise is not a usual finding.

We report the case of a 61-year-old man with a family history of muscle weakness, who presented with congestive heart failure and who was diagnosed with Andersen's disease-related cardiomyopathy.

2. PRESENTATION OF THE CASE

2.1 Case Summary

We report the case of a 61-year-old patient with no noteworthy cardiovascular risk factors, who was being followed for a progressively worsening muscle weakness of an unclear origin, and who underwent two inconclusive muscle biopsies. He had been treated for heart failure (HF) with reduced ejection fraction for about 10 years, the exact etiology of which was not yet known. He was on bisoprolol, sacubutril-valsartan, spironolactone, ivabradine and diuretics at the

time of his admission; he had been fitted with an Implantable Cardioverter Defibrillator (ICD) as a primary prevention measure.

Aside from his sister's similar muscular symptomatology, no indication of consanguinity or heart disease in the family was found following background research.

The patient was admitted to our cardiac intensive care unit with a new onset of congestive heart failure; At presentation, he was orthopneic, had a BP of 90/50mmhg, a heart rate of 80bpm, oedemas of the lower limbs reaching the roots of the thighs, abundant ascites and a spontaneous turgidity of the jugular veins.

His echocardiography showed a dilated LV (Fig. 1) with wall motion hypokinesia and severe systolic dysfunction with an LVEF of 20%, cardiac output was calculated at 2.87 L/min (VTI at 9.6 cm), his RV was also dilated with severe longitudinal systolic dysfunction, he had moderate mitral regurgitation and severe tricuspid regurgitation from coaptation failure.

Clinical and standard workup evaluation revealed normochromic anemia, acute renal failure, increased creatine phosphokinase, and liver enzymes that were likely indicative of congestive hepatopathy.

Following our ICU procedures, the patient was managed for congestion according to the CARRESS-HF protocol, his heart failure profile was labeled INTERMACS 3 with a type III cardio-renal syndrome.

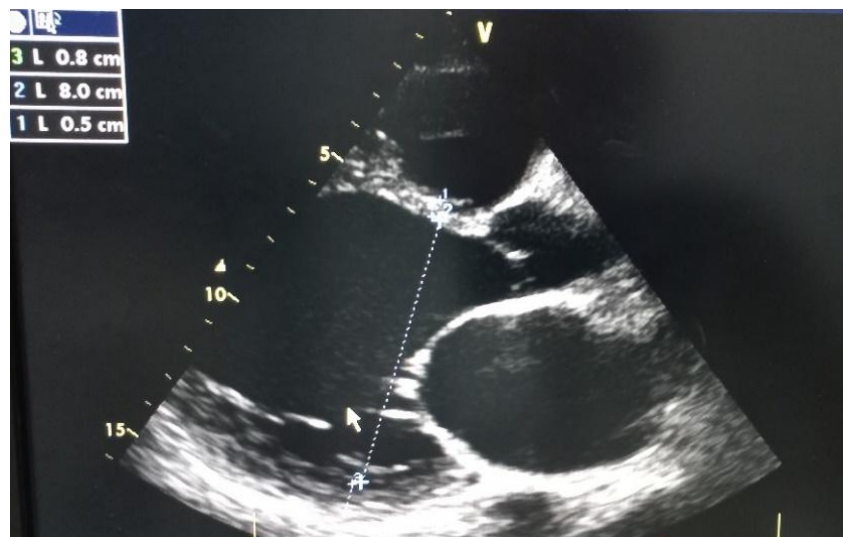


Fig. 1. Transthoracic echocardiography in parasternal long axis view showing dilated left ventricle

Despite high doses of diuretics and vasoactive drugs, the patient's congestion worsened over time. In addition, the patient had a cardiac arrest from which he did not recover when a mechanical circulatory support device was implanted.

2.2 Clinical Investigations

In order to manage this case, we adopted the diagnostic strategy for dilated cardiomyopathy (DCM) recently published in an AHA scientific release [4], starting with an initial workup including (CBC, Electrolytes, HbA1c, TSH, Liver workup, ECG, Echocardiography, HIV serology, and Martial workup); an additional coronary angiogram was performed despite the absence of angina or signs of ischemia and was found normal; a myelogram was performed to evaluate his anemia, showing numerous active histiocytes with no sign of hemophagocytosis, multiple cytoplasmic vacuoles with evidence of dysplasia in the granulomatous lineage-cells. No blasts or bone marrow invasion were observed.

Given the need for inotropes in management of his acute HF, and the complexity of performing a myocardial biopsy (to rule out giant cell myocarditis), we completed the etiological workup with ESR (Erythrocyte Sedimentation Rate), serum and urine protein electrophoresis, a panel of antibodies, and infectious serologies.

Following this assessment, and taking into account the history of familial character of the muscle deficiency, we considered performing a genetic test, a muscular dystrophy assessment and a study of lysosomal diseases. The screening of desalted urine accomplished using thin layer chromatography demonstrated the presence of an increased oligosaccharide excretion, the sample was derivatized with 3-Methyl-1-Phenyl-2-pyrazolin-5-one and subjected to analysis by liquid chromatography tandem mass spectrometry using the method described by Sowell [5], an elevated concentration of glucose tetrasaccharide was noted. Further investigations ruled out an alteration of serum free fatty acids and/or an organic aciduria.

The presence of glucose tetrasaccharide suggests a glycogenosis type II, III or IV; the enzymatic determination of alpha 1-4 glucosidase by spectrophluorometric method in dried blood spots (DBS) was at 6.3umol/Lh

(within the range) thus eliminating Pompe disease (GSD type II).

The genetic study is still in underway, but microscopic examination of a biopsy of his sister's liver revealed abnormal accumulation of amylopectin-like material.

3. DISCUSSION

Glycogen storage diseases (GSDs) are rare genetic disorders of carbohydrate metabolism that manifest clinically as marked fasting intolerance, failure to thrive and hepatomegaly [6].

Laboratory analysis reveals hypoglycemia (with or without ketones), hyperlactatemia, increased liver enzymes and hyperlipidemia. Urinary glucose tetrasaccharide excretions, first described as a biomarker for GSDII (Pompe disease), can also be elevated in patients with other types of GSDs, particularly in type IV GSD commonly known as Andersen' disease [7].

Andersen's disease is an autosomal recessive disorder caused by biallelic pathogenic variants of the GBE1 gene resulting in a deficiency of the glycogen branching enzyme (GBE). As a consequence of its decreased activity, abnormal, more branched and poorly soluble molecules are formed in an amylopectin-like structure (hence the designation amylopectinosis) [8]. These deposits lead to the precipitation of glycogen in the liver and accumulate in body tissues, particularly the heart and liver.

Despite the fact that progressive hepatic cirrhosis is the traditional and most common clinical expression of GSD IV, a review of the literature [9] indicates wide clinical variability.

Andersen's disease exhibits five different phenotypes with varying ages of onset, severity, and clinical properties: the most severe form is the fatal perinatal neuromuscular subtype, a nonprogressive hepatic subtype exists that manifest as hepatomegaly, liver dysfunction, myopathy, and hypotonia. Individuals with this type rarely show progression of liver disease and may not even show cardiac, skeletal muscle, or neurological involvement [1,2].

Another form is the infantile neuromuscular subtype, which is the rarest and has the most variable progression, ranging from onset in the

second decade of life and a mild course of the disease to a more severe and progressive course culminating in death in the third decade; while others may present with more progressive myopathy and, in some cases, dilated cardiomyopathy [1,2].

Since no means are available to replace the deficient enzyme activity, liver transplantation is the only known treatment modality. It has to be borne in mind that transplantation can only remedy the hepatic component of the GSD. In a study of liver transplantation for glycogen storage diseases other than Pompe [10], thirteen patients with type IV GSD were transplanted because of progressive cirrhosis and liver failure. All but one patient had no neuromuscular or cardiac complications during follow-up periods of up to 13 years. Four died between one week and five years after transplantation.

In this case, the diagnosis of GSD IV was assumed by process of exclusion because the clinical condition and hemostasis workup did not allow for cardiac biopsy, along with a post hoc diagnosis of GSD in the sister.

This report is a reminder that in an elderly subject with dilated cardiomyopathy, highly unusual conditions such as GSD merit consideration, particularly when there is evidence of metabolic or muscular involvement in conjunction with a familial pattern. The long-term prognosis of cardiac involvement in GSD IV remains uncertain.

Further research on the genetic, diagnostic, and therapeutic dimensions of GSD with cardiac involvement should provide insight into the pathophysiology and prognosis of the disease.

4. CONCLUSION

Cardiac involvement in Andersen's disease is incredibly rare and difficult to diagnose, especially in geriatric patients with atypical presentations. This case highlights the need to consider glycogen storage disorders in adults with cardiomyopathies with no obvious etiology on standard workup, particularly in the presence of metabolic, muscle, or liver involvement.

CONSENT

The patient's wife gave her informed consent and permitted the writing of this case report.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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