LATE RECOGNITION OF ANDERSEN'S DISEASE IN ADVANCED HEART FAILURE

ABSTRACT

Glucogen storage diseases or glycogenoses are infrequent inherited disorders of carbohydrate metabolism. Andersen's disease is a deficiency of the glycogen branching enzyme that presents with a spectrum of clinical phenotypes, rendering the diagnosis challenging, especially in elderly subjects. A 61-year-old man presented with a history of heart failure from unknown aetiology and muscle weakness; transthoracic echocardiography found showed left ventricular dilatation with thinned walls and severely reduced ejection fraction. He underwent a comprehensive assessment for dilated cardiomyopathy, muscle biopsy was inconclusive, diagnosis of GSD was suspected in view of massive glucose tetrasaccharide excretion and normal alpha-glucosidase activity. Immunohistochemical and ultrastructural confirmation could not be performed in a timely manner, and the patient's condition rapidly worsened, resulting in his demise. A family genetic investigation confirmed the diagnosis as similar condition was identified in his sister.

Keywords: Andersen' disease, glycogenoses, 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 disease (GSD) or glycogenoses are rare hereditary diseases of carbohydrate metabolism. The GSD types are categorized I to IV according to the enzyme that is deficient in each type.

Glycogen storage disease type IV (also named polyglycosan body disease, amylopectionosis 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 heart1. The extent of the disease varies according to the level of 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 common 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 dilated cardiomyopathy.

2. PRENSTATION OF THE CASE

2.1 CASE SUMMARY

This was a 61-year-old patient with no noteworthy cardiovascular risk factors, who was followed up for a progressively worsening muscle weakness from unspecified origin, and who had undergone two inconclusive muscle biopsies. He had been diagnosed with 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.

Background finding did not reveal any notion of consanguinity or heart disease in the family, moreover, his sister exhibited similar muscular symptomatology.

The patient was admitted to our cardiac intensive care unit with a new onset of congestive heart failure; At presentation, he was orthopenic, 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.

Upon clinical and standard workup evaluation on arrival, normochromic anemia, acute renal failure, elevated creatine phosphokinase and liver enzymes probably consistent with congestive hepatopathy were noted.

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.

The evolution was marked by the aggravation of his congestion in spite of high doses of diuretics and vasoactive drugs, the patient presented a cardiac arrest that was not recovered at the time of the implantation of mechanical circulatory assistance devic

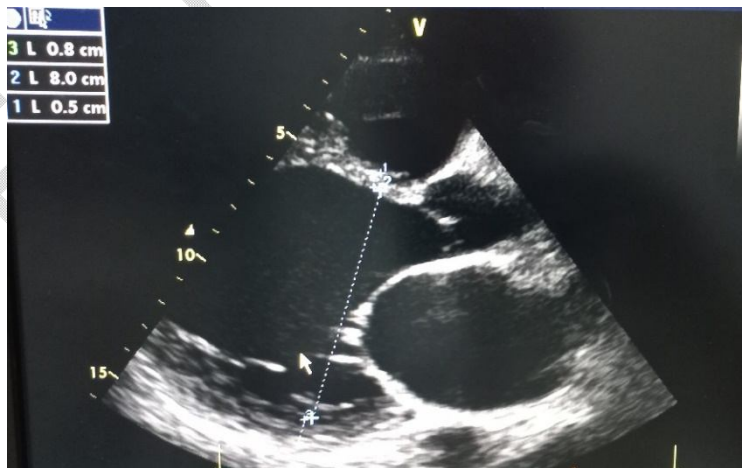

Fig 1: Transthoracic echocardiography in parasternal long axis view showing dilated left ventricle

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 without any evidence of hemophagocytosis or overgrowth cells, in addition to numerous cytoplasmic vacuoles with evidence of dysplasia in cells of the granulomatous lineage. No blasts or bone marrow invasion were observed

Given the need for inotropes for the management of his acute HF, and the unavailability of 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.

At the end of this assessment, and in view of the history of the familial myogenic syndrome, we thought of carrying out a genetic test, muscular dystrophies assessment and a study of lysosomal disease. The screening of desalted urine accomplished using thin layer chromatography demonstrated the presence of an increased oligosaccharide excretion, the desalted urine 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 progress, but microscopic examination of a biopsy of his sister's liver revealed abnormal accumulation of amylopectin-like matter.

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 or commonly known as Andersen' disease, according to a recent cohort studies [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 then 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 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 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.

Yet, the diagnosis of GSD IV was presumed by process of exclusion because the clinical condition and hemostasis workup did not permit cardiac biopsy, and on the basis of a post hoc diagnosis of glycogenosis in the sister.

The present cases emphasize that in an elderly subject with dilated cardiomyopathy, extremely unusual conditions such as GSD deserve to be considered, particularly when there is evidence of metabolic or muscular involvement together with a family background. 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

In conclusion, cardiac involvement in Andersen's disease is extremely rare and is difficult to diagnose, particularly in the elderly with atypical presentations.

This case highlights the need to consider storage disorders in adults with non-ischemic dilated cardiomyopathy of unclear etiology in the presence of liver or muscle involvement.

CONSENT :

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

REFERENCES

1. Magoulas PL, El-Hattab AW. Glycogen Storage Disease Type IV. University of Washington, Seattle; 2019.

2. Kakkar A, Sharma MC, Nambirajan A, Sarkar C, Suri V, Gulati S. Glycogen Storage Disorder due to Glycogen Branching Enzyme (GBE) Deficiency: A Diagnostic Dilemma. Ultrastructural Pathology. 2015;39(4):293-297.

3. Li SC, Chen CM, Goldstein JL, et al. Glycogen storage disease type IV: novel mutations and molecular characterization of a heterogeneous disorder. J Inherit Metab Dis. 2010;33(S3):83-90.

4. Bozkurt B, Colvin M, Cook J, et al. Current Diagnostic and Treatment Strategies for Specific Dilated Cardiomyopathies: A Scientific Statement From the American Heart Association. Circulation. 2016;134(23).

5. Sowell J, Wood T. Towards a selected reaction monitoring mass spectrometry fingerprint approach for the screening of oligosaccharidoses. Analytica Chimica Acta. 2011;686(1-2):102-106.

6. Schreuder AB, Rossi A, Grünert SC, Derks TG. Glycogen Storage Disease Type III. :21.

7. Heiner-Fokkema MR, van der Krogt J, de Boer F, et al. The multiple faces of urinary glucose tetrasaccharide as biomarker for patients with hepatic glycogen storage diseases. Genetics in Medicine. 2020;22(11):1915-1916.

8. ANDERSEN DH. Familial cirrhosis of the liver with storage of abnormal glycogen. Lab Invest. 1956;5:11-20.

9. Moses S, Parvari R. The Variable Presentations of Glycogen Storage Disease Type IV: A Review of Clinical, Enzymatic and Molecular Studies. CMM. 2002;2(2):177-188.

10.Matern D, Starzl TE, Arnaout W, et al. Liver transplantation for glycogen storage disease types I, III, and IV. Eur J Pediatr. 1999;158(2):S043-S048.